SURGICAL PHYSIOLOGY

OF THE

ADRENAL CORTEX

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PREFACE

ENDOCRINOLOGY now occupies a prominent position in surgical study and practice. The manifold potentialities of the pituitary secretions have been spotlighted for many years, but it is only recently that the full force of illuminating investigation has been turned upon the functions of the adrenal cortex. Although more than a score of different adrenocortical hormones have now been isolated and identified, it is evident that the almost incredibly varied activities of these steroids are only beginning to be unraveled. Indeed, the influences of these hormones are second only to those of the pituitary This is in marked contrast to the roles of the pancreas, parathyroids, and thyroid, which organs at the present time are known to secrete only one major endocrine substance

The adrenocortical steroids are of singular interest and importance to the surgeon in the care of his patients. To begin with, major operations would not be possible without adequate cortical activity Furthermore, the use of hormones as therapeutic agents in themselves has been widely exploited Among the processes that are affected by adrenocortical hormones are the metabolism of proteins, fats, carbohydrates, water, and electrolytes, antibody formation and immune reactions, circulatory reflexes and blood pressure, inflammations and bacterial infections, gastrointestinal function, hematopoiesis, and skeletal metabolism, and the peripheral and central nervous systems. Somatic and sexual maturation are particularly affected by adrenocortical hyperactivity The effects of the endocrine organs are doubtless produced in part through the action of hormones on the enzyme systems which regulate various

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J.D.H.

cellular chemical activities. Finally, the adrenal cortices exert important modifying effects upon the function of other endocrine organs.

The purpose in writing this monograph has been to present a series of investigations in surgical endocrinology in which the adrenal cortex has been a major interest. In addition, a résumé of adrenocortical functions is given, the clinical management of adrenocortical tumors and hyperplasia is outlined, and the therapeutic uses of ACTH and cortisone are summarized

The mechanisms of the stress response and associated adrenocortical functions are outlined in Chapter 1. In Chapter 2 the metabolic response to a single operation is examined, and in Chapter 3 the response to multiple operations is presented. Chapter 4 is devoted to the adrenocortical response to extensive burns, and Chapter 5 deals with adrenocortical function in malnourished cancer patients The next three chapters have to do with the laboratory investigation and the clinical management of adrenocortical tumors and hyperplasia Cushing's syndrome, the adrenogenital syndrome, and feminizing syndromes are considered In Chapter 9 is mentioned the current status of adrenalectomy as a treatment for essential hypertension and for metastatic neoplasms of the breast and prostate In Chapter 10 are listed in some detail the mode of action, dosage and routes of administration, and the clinical indications and contraindications for the use of ACTH and cortisone

It is hoped that this volume successfully combines practical therapy for the physiologic surgeon with useful laboratory data for the surgical physiologist

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THE STRESS RESPONSE is of basic importance to the surgeon, and it is germane to begin this discussion of stress with a consideration of the mechanisms by which the stress response is evoked. Stated in the simplest terms, stress results in the release of pituitary adrenocorticotrophic hormone (ACTH) It is probable that the thyroid-stimulating hormone (TSH) and the antidiuretic hormone (ADH) are also released at an increased rate following trauma ACTH stimulates the adrenal cortex to release its hormones, which have manifold capacities to alter body metabolic processes

Types of Stress. Surgical trauma is only one of a large variety of stressful situations which may stimulate the pituitary-adrenocortical axis At the lower end of the scale, minor but definite responses may be elicited by emotional strain. That this can occur in laboratory animals has long been appreciated, and it is now realized that emotional and physical stress can increase adrenocortical activity in man.

Thus the cerebral cortex, whence come the emotions, has a profound influence upon body metabolic processes Through the hypothalamus, it exerts this influence, at least

Chapter I

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in part, by altering the tissue concentrations of hormones which, probably through intermediate enzyme systems, regulate cellular chemical activity.

In addition to traumatic and emotional stress there are other types of stress which are encountered in the management of surgical patients. Pontes and Neves (1) have presented evidence which indicates that adrenal stimulation occurs in the "dumping syndrome" following subtotal gastric resection Fever and infection also are effective activators of the stress response, and an extensive thermal burn evokes the most intense alarm response of any injury that we have studied.

The Stress Mechanism

Activation of ACTH Release in Stress It has been pointed out by Long (2) that any study of the regulation of adrenocortical secretion to a large degree resolves itself into a study of the factors responsible for the release of ACTH from the anterior pituitary. To the understanding of these relationships there will doubtless be added more information concerning the factors, if any, that regulate the formation of ACTH in the gland, since those factors that govern its release are not necessarily synonymous with the factors which govern the formation of the hormone in the gland

During an operation ACTH is released from the anterior pituitary The consensus is that this release may be effected by one of two pathways and possibly by both. The first is by way of the peripheral nervous system and the second is humoral in nature For example, it has been shown that if an extremity is denervated prior to a minor injury there may be no increase in the release of ACTH, as reflected by the level of adrenal ascorbic acid. If the

magnitude of the injury to the denervated extremity is increased, however, there is observed the usual decrease in the adrenal ascorbic acid content (3). In a particularly ingenious experiment, Fortier (4) studied the ACTH response to systemic stimuli (epinephrine, cold, and histamine) and to "neurotrophic" stimuli (sound, immobilization). The adenohypophysis was separated from the hypothalamic centers in rats through transplantation of the gland of a donor into the anterior chamber of an eye of the recipient, who was later hypophysectomized These animals, along with normal controls, were stimulated at weekly intervals and the fall in the circulating eosinophil count was used as an index of ACTH release Epinephrine, cold, and histamine brought about a definite eosinopenia in both normal and grafted animals Sound and immobilization produced a marked fall in the eosinophil count in the intact but none in the grafted animals He considered that these results suggested a dual regulation of ACTH release, one purely humoral, in response to systemic stimuli, and the other probably neurohumoral, mediated by the hypothalamic and hypothalamo-hypophyseal neurohumoral pathways. The evidence for this dual control of ACTH release has been summarized by Hume (5)

The reliability of epinephrine as a stimulator of the pituitary release of ACTH has yet to be defined Previously it was hoped that by using epinephrine as an activator of the anterior pituitary and ACTH as an activator of the adrenal cortex, the functional integrity of both members of the pituitary-adrenal axis could readily be ascertained Unfortunately, while the effectiveness of ACTH as a stimulator of the adrenal cortex has been most gratifying (6), the effectiveness of epinephrine in stimulating the anterior pituitary, as reflected in the evidence of ACTH release

has been disappointing (7, 8, 9). As will be demonstrated in Chapter V, the injection of epinephrine into persons whose pituitary-adrenal axis can respond to ACTH or operation frequently appears to indicate that the responsiveness of either the anterior pituitary or the adrenal cortex is impaired when such is not the case.

In summary, while detectable amounts of ACTH have been demonstrated in the blood following the injection of [illegible]

phrine does not establish that either the pituitary or the adrenal cortex is incapable of an adequate response to operative stress

Salicylates and Pituitary-Adrenal Stimulation

The striking biological effects of cortisone and ACTH are echoed, though somewhat faintly, by the action of salicylates in heavy doses (11, 12, 13, 14). Hetzel and Hine (15) showed that sodium salicylate in doses giving plasma levels of from 15 to 30 milligrams per 100 milliliters depleted the adrenal ascorbic acid to an extent related linearly to the size of the dose This effect was abolished by hypophysectomy They concluded that the therapeutic action of salicylates is mediated through the pituitary and the adrenal glands This view is further supported by the inhibition of experimental serum arthritis by both cortisone and salicylates, and by the reported effect of salicylates in increasing the output of 17-ketosteroids (16).

On the other hand, there is considerable evidence that salicylates oppose the diabetogenic effect of cortisone In defense of their thesis that the therapeutic action of salicylates is mediated through the pituitary and adrenal glands,

Hetzel and Hine cite Sayers' thesis that it is a lowered blood level of the cortical hormones which stimulates the pituitary to release ACTH and they suggest that salicylates increase the utilization of the cortical hormones in the tissues

Whatever the precise nature of the relationship between the salicylates and the cortical hormones may be, further work should clarify the marked therapeutic effectiveness of salicylates in certain conditions which have also responded dramatically to cortisone therapy.

Pituitary-Adrenal Function in the Newborn

The functional capacity of the pituitary-adrenal system in the newborn has been subjected to considerable study. Morel, Bonvallet and Stutinsky (17) found that until the twelfth day of life young dogs are almost completely insensitive to the injection of ACTH in doses which cause a drop in the total eosinophil count of adult dogs. Thereafter the response became progressively greater each day, as evidenced by the fact that the amount of ACTH required to produce an effect diminished each day In a study of infants, Jailer (18) found that the administration of epinephrine to premature infants did not stimulate a significant fall in the total eosinophil count before the ninth day of age, whereas the majority of full-term infants reacted in the first twenty-four hours In general, the smaller the birth weight the greater was the interval before the test became positive The administration of ACTH to all infants produced a significant fall in eosinophils as early as the second or third day of life It was his impression that the premature infant is perhaps less able to cope with alterations in environmental conditions than is the full-term infant

Venning (19), on the other hand, found no difference between the full-term and the premature infant in respect to the urinary excretion of glucocorticoids. Newborn infants excreted small amounts of corticoids that could be detected by both bio-assay and chemical methods, and after the second week of life a gradual increase in the excretion of glucocorticoids was observed. The newborn infant responded to ACTH in the same manner as the adult, with a fall in the eosinophil count and a rise in the urinary corticoids and 17-ketosteroids. It was Venning's impression that at birth the adrenal gland is less responsive to stimulation with ACTH than in the second week of life However, under sufficient stress, such as that of atelectasis, the newborn premature infant was capable of responding with an increased excretion of corticoids

The Rhythm and Regulation of Normal Pituitary-Adrenal Activity

It has been established beyond reasonable doubt that the anterior pituitary responds to humoral factors in adjusting its secretion of ACTH Furthermore, it would appear that these mechanisms function, at least in part, independently of the nervous system (20) If Sayers' hypothesis is correct—and there is much evidence to support it—the pituitary gland responds to a lowered level of cortical hormones by increasing its output of ACTH and vice versa For example, Ingle (21) showed in 1938 that the adrenal cortical hypertrophy induced by stress could be suppressed by the administration of large amounts of cortical extract More recently it has become abundantly clear that the administration of sufficient doses of cortisone suppresses endogenous pituitary-adrenal activity in man This suppression is lessened by the concomitant administration of ACTH In hypophysectomized rats given a uniform intake of ACTH in amounts sufficient to prevent ad-

renocortical atrophy, the additional administration of large amounts of adrenocortical extract fails to diminish the size of the adrenal cortices (20).

Is the output of ACTH in man increased when the blood level of cortical hormones is diminished? Yes, there is evidence that the output of ACTH is increased under such conditions. In studying the blood level of ACTH in man, Sydnor and his associates (22) found no detectable ACTH in the blood of normal non-stressed males, but they did find ACTH in the blood of patients with Addison's disease. Further, it is of interest to note here that an increased blood level of ACTH has been demonstrated in patients with adrenocortical hyperplasia (23).

What is the status of adrenocortical function following hypophysectomy? There is general agreement that in the hypophysectomized animal some residual function of the adrenal cortex remains Moreover, the outer zona glomerulosa appears to be less affected by resection of the pituitary than do the middle zona fasciculata and the inner zona reticularis.

Ingle (20) has noted that the hypophysectomized rat does not show the abnormalities in electrolyte balance which characterize the adrenalectomized rat, and this is of particular interest in the light of the fact that the studies of Deane (24) have indicated that the zona glomerulosa is the zone particularly concerned with the secretion of hormones which primarily influence electrolyte metabolism (Fig 1, p 30) Additional evidence supporting this thesis has been advanced by Wilkins and associates (25), who have suggested that the zona fasciculata is the one primarily concerned with the secretion of carbohydrate regulating hormones The zona reticularis may produce the adrenal androgenic hormones (26, 27). In summary, while there is evidence for and against the postulate that

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produced no further increase in the fall in eosinophils and in the excretion of 17-ketosteroids, though a second infusion on the succeeding day did stimulate a still greater response These findings may prove subject to modification.

It has been found that patients who exhibit little or no response to the intramuscular injection of ACTH frequently do respond adequately to the intravenous administration of this hormone The failure of these patients to respond to the local injection of ACTH appears to be due to the fact that local intramuscular destruction of the hormone occurs (30). The continuous intravenous administration of a given amount of ACTH produces a far greater response than does the intramuscular injection of the same amount of hormone in divided doses (29) Therefore, for economy and for maximal effect, ACTH therapy should be given intravenously when urgently indicated

Renold and his associates found that the intravenous administration of 20 units of ACTH over a period of eight hours produced a mean increase of 6 3 milligrams in the excretion of 17-ketosteroids during a twenty-four hour period in forty-one normal subjects The mean increase in ten persons with Addison's disease was 0 4 milligrams, and following bilateral adrenalectomy the mean increase was 0 1 milligrams in eight patients The total eosinophil count fell an average of 97 per cent in the forty-one normal patients In the patients with Addison's disease there was a mean increase of 4 per cent, and in the adrenalectomized patients there was a mean increase of 5 per cent. These observers noted that following heavy cortisone therapy the iatrogenic adrenocortical insufficiency produced by this hormone did not respond readily to the intravenous administration of ACTH However, when intramuscular ACTH was continued during oral cortisone

the zona glomerulosa functions independently of the anterior pituitary and secretes a hormone which regulates electrolyte balance, there appears to be no doubt that certain stimuli can affect the function of the adrenal cortex independently of ACTH.

What is the Nature of ACTH?

Recent literature pertaining to this subject has been reviewed by Engel (28) Though the precise chemical nature of ACTH has not yet been determined, the data presently available indicate that ACTH is a small molecule containing one or more peptide bonds but probably no free amino groups, although amino and carboxyl groups appear to be essential for its activity. No indisputably chemically pure ACTH has been prepared, and uncertainties will exist concerning the chemical and physical properties ascribed to the hormone until complete and definite purification has been achieved.

The Measurement of Adrenocortical Reserve

While there is increasing doubt concerning the reliability of the epinephrine test as a measure of the functional integrity of the pituitary-adrenocortical system, the more consistent reliability of intravenously administered ACTH as a means of assessing the functional reserve of the adrenal cortex (29) is recognized Although protein shock is not unknown following the intravenous infusion of ACTH, this use of the hormone has proved to be a safe and rather effective means of assessing adrenocortical activity in the vast majority of instances. Renold and his associates (30) have found that 20 units (20 milligrams) of ACTH administered intravenously over a period of eight hours effects the maximum increase in adrenocortical activity, a further increase in the dosage administered

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therapy, the adrenocortices were activated by the administration of the exogenous ACTH, although presumably anterior pituitary inhibition was present.

For practical purposes, therefore, if a preoperative patient suspected of adrenocortical inadequacy does not exhibit at least a 50 per cent fall in the total eosinophil count at the end of eight hours following the infusion of 20 milligrams (20 units) of ACTH, the presumptive diagnosis of adrenocortical insufficiency should be entertained and the patient treated for this condition.

The Physiologic Effects of Adrenocortical Stimulation

General Considerations

It is our purpose in the next few paragraphs to present a brief outline of some of the many physiologic effects of adrenocortical hormones, to be followed by additional discussion of some of the more pertinent of these activities.

The profound influence of adrenocortical hormones upon the intermediary metabolism of carbohydrate and protein, and probably of fat, is well known. Water and electrolyte metabolism are regulated to a very considerable extent through the action and interplay of the hormones of the adrenal cortex and of the anterior and posterior pituitary lobes. The influence of cortical hormones on mesenchymal tissue is striking and has been thoroughly documented during the past several years Lymphoid tissue may disintegrate, and the blood lymphocytes and eosinophils usually diminish in number when cortical hormonal activity is increased by the administration of ACTH or cortisone Moreover, in the acute management of allergic and hypersensitive states adrenocortical therapy has found one of its most useful fields

Inflammatory reactions of almost all types are usually modified by the administration of cortical hormones, and

the course of bacterial infections is often altered. It may be possible to suppress the physiologic effects of bacterial infection without suppressing the multiplication of the bacteria. Nevertheless, cortical therapy for such conditions has both favorable and unfavorable features in that, while the symptoms produced by the infection may be diminished, the body defenses may be so altered by the therapy as to permit the multiplication of bacteria in overwhelming numbers.

The fact that hypotension occurs in adrenal insufficiency and hypertension in certain types of adrenal hyperactivity emphasizes the influence which these hormones have on the vascular system (31), and adrenalectomy is being evaluated as a treatment for essential hypertension.

It is increasingly evident that many types of mental aberration may be associated with hormonal imbalances.

The marked influence of cortical hormone administration on the gastrointestinal tract has been reported by numerous writers, and we have demonstrated a correlation between the diminished gastrointestinal secretion and the increased adrenocortical activity following operation (32).

Finally, adrenocortical function strongly influences the activity of other endocrine organs, notably the pituitary, the pancreas, and the thyroid.

Protein Metabolism. In 1940 Long, Katzin, and Fry (33) noted that adrenocortical extract increased the nitrogen excretion and liver glycogen of the fasted rat, and for some time thereafter it was believed that the increased excretion of nitrogen which followed a major operative procedure was due chiefly to the increase in the secretion of adrenocortical hormones. However, Ingle (34) and Engel (35) later showed that in the adrenalectomized animal maintained on a constant but adequate

dose of replacement therapy an increased nitrogen excretion could still be produced by trauma. They concluded that the presence of a certain "permissive" level of cortical hormone was necessary for the increased metabolism and excretion of nitrogen to occur, but that the increased excretion of nitrogen was not due to an increase in the secretion of hormones per se, though their biologic potency may be altered. Recent work suggests that the increase in nitrogen excretion which follows operation may be related to alterations in thyroid activity.

The availability of cortisone and ACTH have permitted further studies of protein and nitrogen metabolism. It has been found that the marked losses of nitrogen which accompany the administration of ACTH and cortisone can be compensated for by doubling the caloric and protein content of the diet, resulting in a shift from a negative to a positive nitrogen balance. Moreover, Sprague and his associates (36), noting the demonstration by Albright (37) that the negative nitrogen balance of Cushing's syndrome could be altered by the administration of testosterone, found that the negative nitrogen balance produced by 200 milligrams of cortisone daily was reversed by the administration simultaneously of 25 milligrams of testosterone propionate. Whitney and Bennett (38) observed that the catabolic effect of ACTH on nitrogen metabolism could be inhibited by a diet high in potassium, and a similar observation was made by Eliel and Pearson (39) in the treatment of a case of Cushing's syndrome

It will be apparent from the foregoing observations that the role of cortical hormones in protein metabolism is an intricate one, but that these relationships are of practical importance in clinical medicine and surgery

Carbohydrate Metabolism. The importance of adreno-

cortical activity in the maintenance of a normal blood sugar level has long been appreciated After adrenalectomy the carbohydrate reserves of the liver and muscles are diminished and the patient with Addison's disease may die from hypoglycemia. Conversely, an excess of cortical hormones, such as that observed in Cushing's syndrome or after the administration of large amounts of cortisone, is frequently accompanied by a diabetic tendency manifested by glycosuria, an increased blood sugar level, and a diabetic type of glucose tolerance curve. Insulin and cortical hormones are physiologic antagonists, and the diabetes of total pancreatectomy is ameliorated by adrenalectomy. It has long been known that the pituitary-adrenal system has a marked diabetogenic effect in animals (40) and the hypoglycemia associated with the functioning metastases of a tumor of the isles of Langerhans has been effectively combatted by the administration of cortisone (41) Finally, the administration of cortisone will maintain an adequate blood sugar level in patients with Addison's disease in the presence of prolonged fasting

The mechanism by which the cortical hormones maintain an adequate blood sugar level is not entirely clear The adrenal cortex is known to exert a significant influence upon the conversion of protein into carbohydrate and through that mechanism to provide a controlling action over the supply of carbohydrate as a component of the metabolic mixture available for oxidation, the adrenal cortex also tends to regulate the quantity of glycogen present in the liver and the level of glucose in the blood and tissues The influence of cortisone upon the oxidation of carbohydrate in the peripheral tissues may be mediated through enzyme systems

Fat Metabolism. Less is known concerning the in-

fluence of cortical hormones upon fat metabolism than upon the metabolism of protein and carbohydrate. Nevertheless, data are rapidly accumulating which indicate that the cortical hormones do indeed have an important role in fat metabolism. The abnormal distribution of fat in patients with Cushing's syndrome is well known, and recent studies in adrenocortical hyperplasia have shown that when the excessive androgen production (causing the adrenogenital syndrome) is suppressed by the administration of cortisone there may occur such a rapid redistribution and deposition of fat as to cause white striae of the skin beneath the female contours.

A deposition of fat in the liver following cortisone therapy has been noted previously. Lachance and Page (42) have shown that thyroxine and cortisone both promote the accumulation of fat in the brown adipose tissue of intact rats and that their action appears to be synergistic: in adrenalectomized animals the response to the administration of thyroxine was minimal but the response to cortisone administration was comparable to that obtained in intact rats.

Despite the obvious effects of adrenocortical hormones upon fat distribution, the exact nature of the influence of adrenocortical hormones upon intermediary fat metabolism remains controversial. Current work and opinions concerning the role of the adrenocortical hormones in fatty acid synthesis and in ketone metabolism have recently been reviewed by Engel (28).

Electrolyte and Water Metabolism. Promptly following adrenalectomy, or more slowly during the development of Addison's disease, characteristic alterations in the usual state of water and salt metabolism are observed. A marked loss of body sodium (accompanied by water) results in a lowered serum level of this ion In contrast,

the potassium concentration of the serum is elevated, and this is due to a diminished excretion of this ion by the kidney as well as to an increased movement of potassium from the cells into the extracellular space. The normal relationships between the intracellular and extracellular fluid compartments are altered. The loss of sodium from the extracellular compartment results in a loss of water from this compartment, the water being either excreted or transferred into the cells. Total body water is diminished, and this results in a loss of body weight (43, 44, 45, 46, 47, 48).

The patient with adrenocortical insufficiency is unable to excrete administered water at a normal rate and this forms the basis for a part of the Robinson-Power-Kepler (49) water test for Addison's disease Gaunt and his associates (45) believe this to be due to the unopposed action of the posterior pituitary antidiuretic hormone, which is ordinarily antagonized by the adrenocortical hormones. The diminished ability of the kidneys in adrenal insufficiency to excrete an imposed water load is generally considered to be due to an excessive tubular reabsorption of water Under such circumstances water intoxication is readily induced.

Sartorius, Calhoon, and Pitts (50) found that the kidney of the adrenalectomized rat exhibits defects in its capacity to excrete ammonia and titratable acid amounting to, respectively, 50 per cent and nearly 80 per cent of the normal These defects were present under the usual laboratory conditions and under mild and severe acid stress. The findings became apparent within a few hours after adrenalectomy and persisted unchanged for from two weeks to two months These changes, which could be corrected by the administration of DCA or adrenocortical extract, were considered to result from some

specific depression of tubular metabolic activity. As a consequence of these defects in tubular activities, the adrenalectomized animal maintained in otherwise good condition by a high salt intake suffers from mild to moderate acidosis These workers gained evidence, in the form of a diminished cholesterol and ascorbic acid content of the adrenals, that normal animals respond to acid stress with an activation of the adrenal cortex.

The administration of cortisone and/or desoxycorticosterone to adrenalectomized animals results in a marked decrease in the renal excretion of sodium (51), but the influence of cortisone on the renal excretion of water and electrolytes in the intact animal or human being varies considerably from time to time (52).

The fluid and electrolyte changes produced by Cushing's syndrome can be duplicated in most important respects by the administration of ACTH, cortisone, or desoxycorticosterone On the whole, though there are individual variations as noted above there is a tendency to retain sodium, chloride, and water and to excrete potassium Levitt and Bader (48) have demonstrated a shift of water into the extracellular fluid compartment during ACTH and cortisone therapy This redistribution from the intracellular space reached its peak after eight to nine days and then diminished, despite continued treatment. The administration of ACTH and cortisone by these workers produced a progressive increase in glomerular filtration rate and in the filtration fraction

Whereas acidosis may be encountered in Addison's disease, alkalosis is frequently present in hyperadrenocorticism Cooke and his associates (52) have presented evidence which sheds some light upon the possible mechanism by which hypochloremic, hypopotassemic alkalosis is produced

The administration of ACTH, cortisone, or desoxycorticosterone influences also the electrolyte composition of saliva (53) and sweat (54). The concentration of sodium is diminished and that of potassium is increased.

The Adrenal Cortex and Postoperative Fluid Metabolism. Having considered some of the more general aspects of the adrenocortical influence upon the metabolism of salt and water, it is pertinent to describe here certain of the changes which occur in the body fluids and electrolytes following operative trauma. Immediately following a major operation there is a diminution in the urinary volume and in the urinary sodium and chloride content, but the urinary excretion of potassium is increased (55). These changes may represent the net effect of the activity of the adrenal cortex and of the posterior pituitary. The volume of sweat which can be collected in a rubber glove tends to be diminished (56) [illegible] of gastrointestinal secretion which can be aspirated with a Miller-Abbott tube and continuous suction is decreased immediately following operation as compared with control values and with the amount which can be aspirated several days following operation (32).

The practical importance of the diminished urinary output of water and of sodium and chloride is that during this immediate postoperative period the patient cannot excrete these elements at a normal rate, and thus the intravenous administration of these materials should be limited.

The practical importance of the diminished gastrointestinal secretion postoperatively is that the surgeon need not be concerned when the Miller-Abbott tube fails to draw what he considers to be an adequate volume so

long as the abdomen remains soft and flat and the patient has no pain, the bowel is in all likelihood adequately decompressed.

As noted previously, there is a tendency for the serum sodium level to be diminished and for the serum bicarbonate level to be somewhat increased following operation. The volume of the extracellular fluid is increased, presumably at the expense of the intracellular fluid compartment. These changes are considered to be related to an increase in adrenocortical activity.

Streeten and Ward-McQuaid (58) have studied thirteen patients with paralytic ileus in an attempt to discover the relationship of adrenocortical hyperactivity and of potassium and chloride deficiency to the development of this condition, but their findings were not conclusive. There is no question but that paralytic ileus is frequently associated with a potassium deficiency, but it remains to be demonstrated whether or not this ileus can be the result of an increased adrenocortical activity in the absence of a potassium deficit.

The Cardiovascular System. As mentioned, striking changes in the cardiovascular system are observed in adrenal insufficiency There is a fall in the arterial blood pressure, obvious peripheral collapse, a decrease in circulating blood volume, and a decline in the cardiac output Conversely, in hyperadrenocorticism, such as occurs in Cushing's syndrome, there may be found hypertension, an increased blood volume and red cell mass, and a florid appearance—findings which can be duplicated in large measure by the administration of ACTH or cortisone As noted, such relationships have stimulated interest in adrenalectomy as a treatment for essential hypertension

Cortical hormones have been shown to have an important influence on capillary resistance. Robson and Duth-

rie (59) observed that the infliction of various types of tissue damage and the application of various other forms of stress may be followed by an increase in capillary resistance. The administration of ACTH also decreased capillary fragility, as measured by a negative-pressure method. Kramar and Simay-Kramar (60) demonstrated a consistent pattern of alterations in the capillary resistance (fragility) following sham adrenalectomy and adrenalectomy. Following sham adrenalectomy there was a more or less pronounced increase in capillary resistance during the first day, a critical drop at the end of the first or during the second week, then a state of pathologically low resistance lasting about two weeks, and finally a period of recuperation The entire phenomenon, which they termed "capillary crisis," required about one month After adrenalectomy only the second and third phases of the above pattern were seen; that is, the initial rise was absent and the capillary resistance remained at low levels during the entire period of observation (up to nine months) A study in the late postoperative period showed that cortisone promptly restored the capillary resistance but, surprisingly, ACTH did not The administration of cortisone to the sham operated animals, or to the merely anesthetized animals before the procedures, abolished the usual phases of the capillary crisis Desoxycorticosterone acetate and ACTH did not do so in the doses employed

Robson and Duthie took their study a step farther and treated patients with thrombocytopenic purpura. Definite clinical remissions were obtained on three occasions These workers suggested the use of the capillary resistance method as a measure of the response to stimulation of the adrenal cortex As will be seen in Chapter X, numerous workers have utilized cortisone and ACTH in the therapy of thrombocytopenic and hemolytic conditions with gratifying results

long as the abdomen remains soft and flat and the patient has no pain, the bowel is in all likelihood adequately decompressed.

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the normal range, as measured by an over-all adrenal response index which was the mean of the sum of the changes in the six urinary and blood variables. These schizophrenics, however, showed qualitative abnormalities of response as compared to normal persons, in terms of the ratios of their various urinary indices.

These findings are but indicative of the mass of data being accumulated which indicates that the total metabolism of the human organism must be viewed as a single unit and, further, that mental diseases probably represent definite physicochemical aberrations that will eventually be defined

Mesenchymal Tissues The adrenocortical hormones have a marked effect upon the physiologic processes involved in "collagen diseases," and these effects are discussed in some detail under the section dealing with ACTH and cortisone therapy

Inflammations The administration of cortisone and ACTH has a modifying influence on the course of inflammatory processes, but the precise site of action of these agents in diminishing or suppressing the usual evidence of inflammation is not certain Cooke and Smith (62) believe that the fact that cortisone can suppress the inflammatory reaction irrespective of the causative agent is due to the fact that cortisone can nullify the usual increase in capillary permeability and that, thus, the site of cortisone's action is vascular

It is by no means certain that it is desirable to utilize cortisone to prevent the usual body reaction to an inflammatory agent, though under certain conditions such a suppression may be indicated

Allergic (hypersensitivity) Syndromes The majority of investigators agree that the administration of adequate amounts of ACTH and/or cortisone to patients with al-

The Nervous System Recent knowledge of the influence of the adrenal steroids on mental processes has instilled new hope that the mysteries surrounding mental disease will ultimately be dispelled. The fairly distinctive personality of patients with Addison's disease on the one hand, and of patients with Cushing's disease on the other, have indicated that the adrenocortical steroids do in fact influence mood The use of cortisone and ACTH has further strengthened these impressions by virtue of the fact that these agents produce euphoria in some patients, and in these and in other patients depression may ensue upon withdrawal of the drug. Certain individuals become actually psychotic during the administration of these agents, and certain psychotic patients became lucid while on therapy.

Hoagland (61) investigated patients with personality disorders and found that approximately two-thirds of a large group of chronic schizophrenic patients showed unresponsivity of the adrenal cortex to several psychological and physiological stresses, in contrast to normal controls Test injections of adrenocortical extract produced similar responses in the measured indices in both control and patient groups, indicating that the peripheral organs acted upon by the adrenal steroids responded normally As compared to the controls, two-thirds of the schizophrenic patients were unresponsive, by the criteria used, to 25 milligram test injections of ACTH, indicating that the unresponsivity lay at the level of the target organ for ACTH, namely, the adrenal cortex itself. Nevertheless, larger doses of ACTH did activate the patients' adrenals In contrast to psychotic patients, psychoneurotic individuals displayed normal responses to ACTH One-third of the schizophrenic patients had adrenal responses to the imposed stresses and to ACTH which were within

(65) have stated that such spontaneous infections are possibly due either to a flare-up of foci which are ordinarily suppressed by the patient's defense mechanisms or to the taking root of "non-pathogens" in hosts whose defense mechanisms are impaired by the hormone. Antopol and Quittner (66) have pointed out that cortisone may so alter the reactivity of the host that some tissues will resist a degeneration-producing stimulus while others will react to produce unusually severe degeneration and necrosis

These workers have proposed that cortisone be given to detect the presence of reservoirs or of subclinical infections in animals, for cortisone permits the growth and multiplication of organisms in certain animals which are normally resistant to the multiplication of these bacteria

Only under very special conditions is cortisone or ACTH therapy indicated in the management of severe infections (Chapter X).

Enzyme Systems There is increasing evidence that the adrenocortical hormones have a decided influence upon enzymes and thus upon the cellular processes regulated by enzymes Several reviews of the relationships between adrenocortical hormones and different enzymes have been published (67), and it is important to appreciate that such studies indicate a direction in which further advances in our knowledge of surgical physiology are likely to lie

Hematopoietic System Thorn and his associates (68) demonstrated in 1948 that an increase in adrenocortical hormones, produced by the administration of ACTH, results in a significant fall in the total eosinophil count There is also a fall in the lymphocyte count and frequently a rise in the number of polymorphonuclear leucocytes other than eosinophils.

lergic manifestations results in prompt improvement. Such therapy may allow a permanent remission in acute allergic reactions, but the more chronic allergic conditions, such as bronchial asthma, are not cured and tend to relapse.

Bacterial Infections. In 1950 Kass, Ingbar, and Finland (63) reported their studies of the effect of ACTH and cortisone therapy in pneumonia. They found that the fever and toxic symptoms were abolished even in patients in whom the blood culture remained positive for pneumococci. Thus, there was no evidence of a bactericidal effect, and the date of the appearance and magnitude of the rise in anti-pneumococcal antibodies and cold agglutinins were unaffected by the ACTH and cortisone. Moreover, the rate of resolution of consolidated lobes was not accelerated.

Studies such as these inaugurated a new era in the study of the relationships between bacteria and host, in that an agent had been found which prevented the bacteria from injuring the cells of the host but which allowed *the bacteria to continue to multiply* In the same year Mogabgab and Thomas (64) reported their studies concerning the effect of cortisone on experimental infection with Group A streptococci in rabbits These workers injected Group A streptococci into the skin of rabbits, some of which were treated with cortisone in doses of 50 milligrams per day and others kept as controls without cortisone therapy In the treated group a fatal septicemia developed in all animals, whereas in the controls, who received the same dose of bacteria but no cortisone, there were no deaths

Since these early studies, so-called "spontaneous" infections have been reported from time to time in patients receiving cortisone therapy Antopol and his associates

terior pituitary, the posterior pituitary, and the pancreas on the other, have been alluded to. Important reciprocal influences exist between adrenocortical activity and thyroid activity, and these influences exert an effect upon the intermediary metabolism of protein, fats, and carbohydrates

The effect of adrenocortical hormones upon the eosinophils has been studied by Godlowski (69) and by Padawer and Gordan (70) These workers agree that the eosinopenia results from eosinolysis. Godlowski points out that lysis of the other polymorphonuclear cells is actually masked by their mobilization initiated by the cortical steroids through some unknown mechanism. The lymphocytes are considered to be less sensitive to the lytic action of the hormones than are the eosinophils.

The uses of ACTH and cortisone in such conditions as aplastic anemia, agranulocytosis, thrombocytopenic purpura, and hemolytic anemia are discussed in Chapter X.

Work Performance. Ingle and his collaborators (71) have conducted extensive studies of muscle work performance by adrenalectomized animals, and such investigations have clinical value in view of the increasing number of patients in whom total adrenalectomy is being done for various disease states. They found that the continuous intravenous infusion of glucose improved work performance but that this improvement was correlated more closely with total fluid load than with the dose of glucose Cortisone administered either subcutaneously or by continuous intravenous infusion improved work performance but was less effective than hydrocortisone administered by the same route However, neither compound E nor compound F was as effective as adrenocortical extract administered by continuous intravenous infusion Such findings suggest that full adrenocortical activity is not accounted for by the actions of either cortisone or compound F and draw attention again to other factors such as those in the "amorphous fraction" which has a powerful effect on water and salt metabolism

Effects on other Endocrine Organs Relationships between the adrenal cortex on the one hand, and the an-

time of the blood. As discussed in the preceding chapter, the evidence indicates that epinephrine and neural impulses simultaneously stimulate the anterior pituitary to release ACTH and, possibly, thyroid stimulating hormone (TSH) into the blood stream. The ACTH activates the adrenal cortex to secrete increased amounts of the adrenocortical hormones, and these hormones affect the metabolism of carbohydrates, proteins, and fats, the body fluids, antibodies, and all the other physiologic processes previously outlined.

A presentation of the results of a series of experiments designed to examine the adrenocortical reaction to a single operation in the human being follows.

Methods

The patients studied were general surgical patients on the wards of the Hospital of the University of Pennsylvania When an individual was selected for the project he was placed in a special cubicle or, later in the study, in the metabolic ward. During the preoperative control period, which generally lasted from three to seven days, the patient was placed on a standard metabolic diet of natural foodstuffs of approximately 150 grams of protein and 2100 calories The length of the control period was limited by clinical considerations. Though a larger dietary intake would perhaps have been desirable, the program had the merit of permitting a constant protein and caloric intake to be administered—orally before operation, intravenously during the first three postoperative days, and then orally in the later postoperative period. Moreover, the administration of the same intake to each patient, although varying fairly widely between individuals when expressed as calories and grams of nitrogen per kilogram

Chapter II

THE EFFECT OF A SINGLE OPERATION AND OTHER FORMS OF STRESS UPON ADRENOCORTICAL ACTIVITY: CORRELATION WITH CERTAIN OTHER ASPECTS OF METABOLISM

IN 1932, CUTHBERTSON (72) made the unexpected observation that the mere fracture of a long bone was accompanied by an increase in the urinary excretion of nitrogen and calcium which persisted for many weeks In the years that followed it was shown by others that a severe fracture may be followed by physiologic changes which suggest those of hyperadrenocorticism.

Following major surgery there is observed a characteristic pattern of metabolic response which is basically similar whether the operation be an orthopedic, gynecologic, neurosurgical or other procedure. When the patient is subjected to operation, epinephrine is promptly released through stimulation of the adrenal medulla, and this hormone produces the following well-known sympathomimetic effects A rise in general blood pressure and an increase in the force and output of the heart, hyperglycemia, resulting from the mobilization of carbohydrate from the labile stores in the liver and ensuring an adequate supply of fuel, an increased oxygen carrying capacity of the blood due to the discharge of red cells *from the spleen*, bronchiolar dilatation and an increased rate and depth of respiration, and a shortened coagulation

During the control period twenty-four hour collections of urine (and of feces in the nitrogen balance studies) were made. Total eosinophil counts (68) and the urinary excretion of corticoids (lipid-soluble reducing substances) (73), total neutral 17-ketosteroids (74), nitrogen, and preformed creatinine were measured. In our laboratory the normal range for the urinary excretion of corticoids is from 5 to 8 milligrams per 24 hours. The normal excretion of 17-ketosteroids has ranged from 6 to 15 milligrams per 24 hours in females (average about 9 milligrams) and from 7 to 20 milligrams per 24 hours in males (average about 14 milligrams). In normal subjects the daily variations in the excretion of corticoids and 17-ketosteroids have been relatively small in any given person. In patients who have recently been operated upon or are otherwise ill, there may be a considerable day to day variation in the excretion of both moieties, though an explanation for these variations is not always apparent.

The volume and the electrolytic composition of urine and of sweat were examined in a number of patients, and these results were correlated with alterations in adrenocortical activity, as was the volume of gastrointestinal secretion which could be aspirated with constant suction through a Miller-Abbott tube before and following operation.

Results

Total Eosinophil Counts

Total Eosinophil Counts Following a Major Operation. In Figure 2 are shown a series of total eosinophil counts before and following cholecystectomy. The ACTH-eosinophil test of the adrenocortical reserve was performed several days preceding the operation. It may be

of body weight, was not so disproportionate when expressed on the basis of kilograms of "lean body mass" The intravenous alimentation in all experiments reported in these studies was accomplished with protein hydrolysate, 7.5 per cent alcohol, and glucose solutions. While

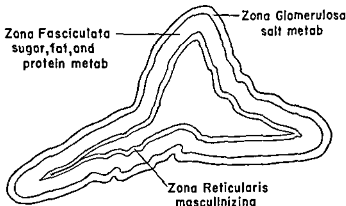


Figure 1 The Adrenal Cortex There is evidence which indicates that the three zones of the adrenal cortex may have separate functions The zona glomerulosa appears to be primarily concerned with salt and water metabolism The zona fasciculata probably secretes hormones which have to do with the metabolism of glucose, fat, and protein The zona reticularis is thought to secrete most of the adrenal androgens which produce the masculinization of the adrenogenital syndrome In essence, the adrenal cortex may represent three organs in one

the nitrogen balance studies were of particular interest in certain patients who will be discussed, an equally important nutritional objective was to maintain a constant dietary intake in view of the possible effect which variations in the dietary intake might have upon the level of adrenocortical activity.

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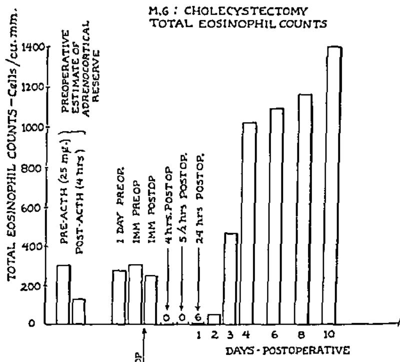


Figure 2 M G Cholecystectomy—Total Eosinophil Counts In the preoperative period the administration of 25 milligrams of ACTH intramuscularly produced a fall to a level which was less than 50 per cent of the preinjection eosinophil count However, the stimulus of the surgery was greater than that produced by the intramuscular injection of 25 milligrams of ACTH, and four hours following operation the total eosinophil count had fallen to zero By the third postoperative day the count had risen to levels exceeding those present preopera- … rising … The … ictory … ie response of the patient to operation. (Hardy, J. D, and Ravdin, I S *Ann Surg*, *136* 347, 1952. J. B Lippincott Company).

seen that four hours following the injection of 25 milligrams of ACTH the total eosinophil count had fallen to less than 50 per cent of the preinjection level. Thus it was to be expected that this patient's adrenocortical reserve would be adequate to sustain the operation Following surgery there was an initial fall in the eosinophil count to zero, but at the end of twenty-four hours a few eosinophils were beginning to appear and on the tenth postoperative day a count of 1400 cells per cubic millimeter was found. This very high level was indicative of the rebound in the total eosinophil count which is commonly observed during the intermediate postoperative period when by measurements of steroid excretion the previously elevated adrenocortical activity can be shown to be diminishing. At the end of from two to three weeks following an operation of this type the total eosinophil count may be expected to return approximately to preoperative control values.

This general type of eosinophil reaction, then, is characteristic of the response of the eosinophil count to operation in previously healthy subjects

Effect of Emotion and of Fever on the Total Eosinophil Count We have not infrequently observed a fall in the total eosinophil count on the morning preceding a scheduled major operation when the patient had not yet received preanesthetic medication, and the effectiveness of emotional stress as a stimulus of increased adrenocortical activity has been documented by others In Figure 3 are shown the effect on the eosinophil count of a physiologic episode whose cause was not fully determined, of operation, and of a febrile reaction On the morning of the scheduled operation patient B. H. showed a low total eosinophil count, and dissolution of the remaining cells appeared imminent. This unusual and interesting finding

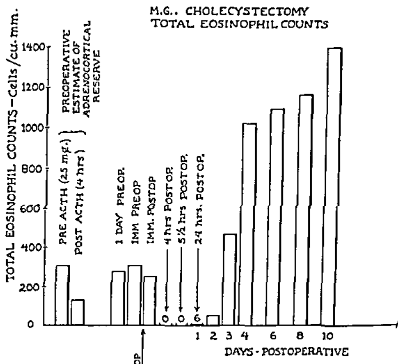


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was telephoned to the ward staff, who noted that the patient's blood pressure had fallen to 80/60, and the operation was cancelled Three days later the patient withstood operation without event and four hours following the procedure the total eosinophil count had fallen almost to zero. Two days after the operation the total eosinophil count had begun to approach preoperative levels, but on the following day the temperature spiked to 103 6° rectally and the total eosinophil count again fell to zero.

It is important to appreciate that almost any type of strain to which the individual is subjected may result in an activation of the pituitary-adrenal system to produce the alarm response Among other stimuli are heat, cold, harsh sounds, a salt load, an acid load, and the "dumping syndrome" following subtotal gastric resection

Total Eosinophil Counts Following Adrenalectomy (95%). When a patient is subjected to bilateral adrenalectomy, the fall in the total eosinophil count which characteristically follows other operations is not observed Instead of falling, the total eosinophil count may actually rise following the removal of the second adrenal gland. In Figure 4 the total eosinophil counts in a patient who had a cholecystectomy are compared with those in patients who had almost all of their adrenal tissue removed Following cholecystectomy (patient M G) the count fell to zero In patient Sch , who had a subtotal adrenalectomy, the total eosinophil count did fall to less than 50 per cent of the preoperative level, but this patient required no replacement therapy in the postoperative period and therefore presumably had considerable residual functioning adrenal tissue On the other hand, patients Lee and C H exhibited no fall whatever in the total eosinophil count following bilateral and almost total adrenalectomy, in fact, these patients exhibited a con-

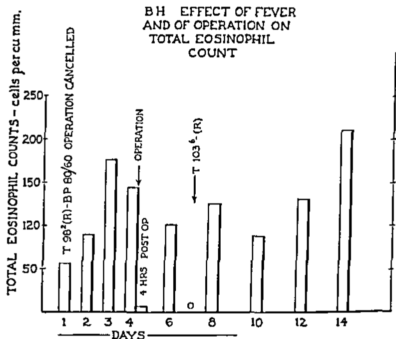


Figure 3 B H Effect of Fever and of Operation on the Total Eosinophil Count On the first day of the study a count taken immediately before the anticipated operation showed only a few cells, and the cells which were present appeared to be disintegrating Concurrently it was noted that the patient's blood pressure had fallen to 80/60 and the operation was cancelled On the fourth day the operation was performed, the preoperative count was approximately 157 cells per cubic millimeter and the count four hours following operation was almost zero By the sixth day the count had risen to approximately 120 cells per cubic millimeter On the following day the temperature spiked to 103 6° F (rectally), and this resulted in a prompt fall in the total eosinophil count to zero This chart represents the adrenocortical response to three types of stress, the initial one being unknown, the second being that of operation, and the third being that of the febrile episode

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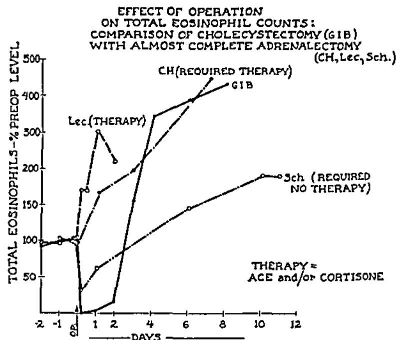


Figure 4. Effect of Operation on Total Eosinophil Counts Comparison of Cholecystectomy with Almost Complete Adrenalectomy The count of the patient who had a cholecystectomy (represented by the solid line) showed a prompt fall to zero after operation, followed two days later by a marked rebound to levels which far exceeded those present preoperatively The patient who had an almost complete adrenalectomy but who required no replacement therapy (Sch) showed a postoperative fall in the total eosinophil count to a level which was less than 50 per cent of that obtaining preoperatively This indicated that a fair amount of functional adrenocortical tissue remained and, as noted, this man required no replacement therapy On the other hand, the patients Lec and C H required therapy following subtotal adrenalectomy, and in both of these patients the total eosinophil count exhibited no fall following operation On the contrary, the count began rising immediately following operation (Dr Harold A Zintel performed the adrenalectomies)

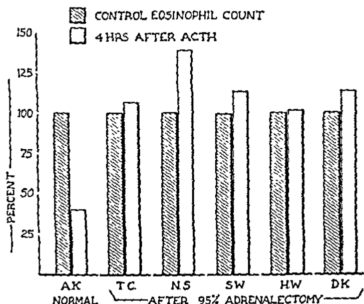


Figure 5 Effect of ACTH (25 milligrams) on Total Eosinophil Counts after Adrenalectomy The normal subject exhibited the expected fall in the eosinophil count following intramuscular ACTH. The adrenalectomized patients exhibited no fall in the count following ACTH and generally showed a slight rise

tinuing rise in the total eosinophil count. Both required replacement therapy promptly in the postoperative period.

The Effect of ACTH (25 milligrams) on the Total Eosinophil Counts after 95% Adrenalectomy and in a Normal Subject Following almost total or total adrenalectomy, the intramuscular injection of ACTH produced no fall in the total eosinophil count and, indeed, in four of five adrenalectomized patients shown in Figure 5 the administration of ACTH actually was followed by a slight rise. The same amount of ACTH intramuscularly

produced in the normal subject (A. K.) the usual greater than 50 per cent fall in the total eosinophil count. Though certain of the adrenalectomy patients had required replacement therapy in the immediate postoperative period several weeks earlier, none of the five patients was on replacement therapy at the time the test was performed. This finding of a slight increase in the total eosinophil count following the administration of ACTH in adrenalectomized patients is of interest in light of the recently reported finding of Thorn and his associates (30) that ACTH given intravenously in patients with Addison's disease and following total adrenalectomy produced an average slight *rise* in the total eosinophil count.

The data emphasize the quantitative limitations of the ACTH-eosinophil test as a measure of the adrenocortical reserve. These patients obviously had sufficient residual adrenocortical tissue to maintain homeostasis in the absence of unusual demands, though certain of them required replacement therapy when they developed the slightest upper respiratory infection. Yet, the ACTH-eosinophil test was not sufficiently sensitive to demonstrate the residual functioning adrenocortical tissue, or perhaps the adrenal remnant was already responding maximally to the ACTH from the patient's own pituitary gland and thus was unable to respond further to the injected ACTH

Correlation of Total Eosinophil Counts with Urinary Corticoid Excretion. The values for the total eosinophil count and the urinary excretion of corticoids before and after operation in four patients are presented in Figure 6 In each patient there is a consistent inverse relationship between the two curves, both of which tend to return to the preoperative levels at approximately the same time Patient Cun. exhibited a prolonged increase in the excretion of corticoids, and the total eosinophil count

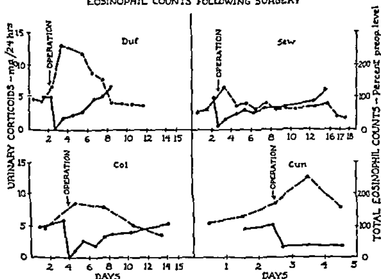


Figure 6. Correlation of Changes in Urinary Corticoid Excretion with Total Eosinophil Counts Following Surgery In each patient there was a reciprocal relationship between the total eosinophil count and the urinary excretion of corticoids The increase in the excretion of corticoids following operation, indicating an increase in adrenocortical activity, was accompanied by a fall in the total eosinophil count to levels either at or approaching zero In three of the four patients the excretion of corticoids and the total eosinophil count tended to return to the preoperative base line at approximately the same number of days following the operation The fourth patient (Cun) had a stormy postoperative course following a colon resection, and at the time the study was terminated the urinary excretion of corticoids was still elevated and the total eosinophil count was still depressed (Hardy, J D, Richardson, E M, and Dohan, F C *Surg, Gynec & Obst*, *96* 448, 1953, by permission of Surgery, Gynecology and Obstetrics)

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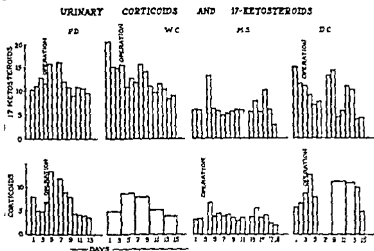


Figure 7 Urinary Corticoids and 17-ketosteroids A Comparison In all four patients there was an increase in the urinary excretion of corticoids following the major operation. In only two of the patients was the excretion of 17-ketosteroids increased following the operation The measurement of urinary corticoid excretion is considered to be a more reliable index of the alteration in adrenocortical activity immediately after operation than is the measurement of 17-ketosteroids (Hardy, J D, Richardson, E. M, and Dohan, F C. *Surg, Gynec & Obst*, 96 448, 1953, by permission of Surgery, Gynecology, and Obstetrics)

cretion of 17-ketosteroids. Therefore, the measurement of urinary corticoids appears to afford more reliable information concerning the increase in adrenocortical activity following operation than does the measurement of urinary 17-ketosteriods. The measurement of blood corticoid levels (page 50) may supply important complementary information The fact that the urinary excretion of 17-ketosteroids in normal subjects is consistently increased by the injection of ACTH but not by operation may reflect the influence of the liver upon the metabolism of steroids.

remained depressed for a correspondingly prolonged interval. This inverse correlation between the urinary excretion of corticoids and the total eosinophil count in the immediate postoperative period has been found to be a consistent one in patients undergoing major operations. Nevertheless, this close relationship observed in the early postoperative period is less apparent in the late postoperative period in many patients. For example, we have found in other patients followed for many weeks after operation that the intervention of a wound infection which produces a secondary rise in the urinary excretion of corticoids may be accompanied by little or no decrease in the total eosinophil count. Thus, in some patients the total eosinophil count appears to escape partially from the *influence of the adrenocortical hormones late in the convalescent period.* We have found no consistent correlation between the total eosinophil count and the urinary excretion of 17-ketosteroids

Corticoids vs 17-ketosteroids Following a Single Operation

In Figure 7 is shown the excretion of corticoids and of 17-ketosteroids before and after operation in four patients All exhibited a sharp increase in the urinary excretion of corticoids following operation. From left to right, the first two patients had subtotal gastric resection, the third a common duct exploration, and the fourth a segmental colon resection Two of the four patients exhibited an increase and two a decrease in the urinary excretion of 17-ketosteroids following operation

The findings in these four patients are in accord with our findings in many other patients similarly studied Operative trauma is almost always followed by an increase in the urinary excretion of corticoids, but it is not consistently followed by an increase in the urinary ex-

Correlation of Adrenocortical Activity with Certain Other Aspects of Metabolism Following a Single Operation

It is helpful, in visualizing the integration of these various facets of the physiologic response to operation, to view a composite of the parts The following three case studies are presented for this purpose.

Patient P. D., Gastric Resection

Clinical Data. Three weeks prior to the beginning of the study whose results are presented in Figure 8, this fifty-three-year-old man had been admitted with a perforated duodenal ulcer which had been closed surgically. His convalescence had been uneventful and he had elected to remain in the hospital and have a gastric resection performed as management for his duodenal ulcer which had proved refractory to medical management During the preoperative control period he received 2100 calories and 150 grams of protein each day and was in positive nitrogen balance.

Laboratory Data The urinary excretion of corticoids and 17-ketosteroids was within normal limits, and the urinary excretion of preformed creatinine was at a level which was consistent with the muscle mass The preoperative total eosinophil counts were not remarkable.

Following operation there was an increase in the urinary excretion of corticoids, 17-ketosteroids, and of preformed creatinine, associated with a fall in the total eosinophil count to zero and the appearance of a negative nitrogen balance. By the end of the fifth postoperative day the values had in general returned to the preoperative control levels, and thereafter most of these values tended to continue their downward or upward courses, respectively Specifically, following the early postoperative period there was a tendency for the uri-

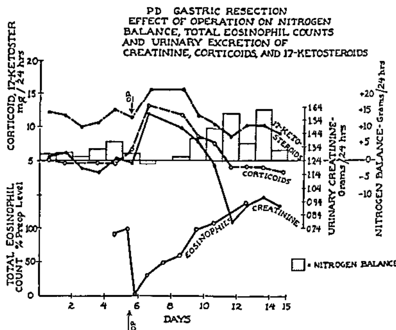


Figure 8 P D Gastric Resection, Effect of Operation on Nitrogen Balance, Total Eosinophil Counts and Urinary Excretion of Creatinine, Corticoids, and 17-ketosteroids. The fall in the total eosinophil count following operation was associated with an increase in the urinary excretion of nitrogen (note negative nitrogen balance), creatinine, corticoids, and 17-ketosteroids Approximately five days after operation the levels of excretion of these various moieties had returned to the preoperative base line and—in the case of the corticoids, creatinine and total eosinophil counts—had fallen below the base line The metabolic changes which follow the usual gastric resection are not as extensive as are those which follow an extensive burn or a thoracoplasty In other words, in the graded scale of trauma, a gastric resection represents only a moderate injury to the patient (Hardy, J D, and Ravdin, I S *Ann Surg*, *136* 353, 1952)

is suggestive evidence that postoperative alterations in the excretion of creatine and creatinine may reflect alterations in thyroid activity (76, 77, 78).

Patient W. C.: Gastric Resection

Clinical Data. This sixty-three-year-old man was admitted with a chronic duodenal ulcer which had been refractory to medical therapy. The preoperative state of nutrition was considered to be adequate, his weight being 151 3/4 pounds (69 kilograms) and his height 68 inches (173 centimeters).

Laboratory Data The results of this study are presented in Figure 9 Preceding the operation he was in slightly positive nitrogen balance, and the urinary excretion of corticoids and 17-ketosteroids was within normal limits The urinary excretion of creatinine was compatible with the magnitude of the muscle mass Following operation there occurred the usual increase in the excretion of corticoids, nitrogen, and creatinine The total eosinophil count decreased, as did the excretion of 17-ketosteroids. By the end of the sixth postoperative day the increased excretion of nitrogen, corticoids, and creatinine had returned to normal levels and was beginning to exhibit the usual mild subnormal phase The nitrogen balance had again become positive, and the total eosinophil count was approaching normal values

Comment It is to be noted that this patient too exhibited a return of most of the measured physiologic activities to control levels within about six days following gastric resection While it is customary to think of this operation as representing major trauma, it will be seen in Chapter IV that following an extensive full-thickness thermal burn adrenocortical activity may not return to normal levels for weeks following the injury

The physiologic response to gastric resection in patient P D was somewhat less robust than that exhibited by

nary excretion of corticoids and 17-ketosteroids to decline slightly from the preoperative control levels The urinary excretion of creatinine increased briefly following operation but in the postoperative period there was a sharp fall in the level of this excretion. After the fall to zero immediately following operation, the total eosinophil count gradually approached and eventually exceeded the preoperative levels Following the slight negative nitrogen balance there was a sharp increase in the retention of nitrogen over and above that observed before operation.

Comment The findings in this patient are typical of those commonly observed following operations of this magnitude, with but two exceptions. First, an increase in the urinary excretion of 17-ketosteroids has not occurred consistently in the patients that we have studied and, second, following operation this patient exhibited only a mild negative nitrogen balance, much less than is commonly observed This was probably due to the fact that he had undergone an operation about three weeks earlier, at which time most of the readily mobilizable nitrogen may have been excreted It is well known that the starved patient or animal does not exhibit the usual generous increase in the urinary excretion of nitrogen following trauma

We have found that major operations frequently result in an increase in the urinary excretion of creatinine, a portion of which is due to an increase in creatine excretion These findings would appear to reflect definite alterations in the metabolism of these substances in the muscle mass and, indeed, it would be surprising if the largest metabolically active mass of the body, the musculature, did not enter into the stress reaction Other examples of the participation of the muscle mass in the stress reaction are to be found in studies of electrolyte and carbohydrate metabolism following trauma. There

of the operation This was of particular interest in view of the fact that he exhibited a marked increase in nitrogen excretion, for White and Dougherty (76) have obtained evidence indicating that the thyroid is particularly effective in mobilizing muscle nitrogen Patient P. D showed only a very small negative nitrogen balance (because he had had a previous operation two weeks earlier?), and his thyroid activity appeared to have been depressed by the operative procedure, as indicated by the thyroid uptake of radioiodine. We have previously published studies which suggested that thyroid activity is increased following operation (77), and recent studies by Goldenberg and Hayes (78) have added further support to this possibility.

Patient D. C Segmental Colon Resection

Clinical Data This fifty-one-year-old man was admitted with a carcinoma of the sigmoid colon The preoperative state of nutrition was considered to be satisfactory (weight 176 pounds, 80 kilograms, height of 72 inches, 183 centimeters) A segmental colon resection was performed uneventfully, but he ran a moderately febrile course for some days following the operation. Moreover, the emotional reaction to the stress of operation was an intense one During the first ten days following operation he lost 10 pounds (4 5 kilograms).

Laboratory Data· The results are presented in Figure 10 Surprisingly, the total eosinophil count did not fall to zero following the operation It fell to approximately 60 per cent of the preoperative level and then continued to be depressed throughout the duration of the study, though at the end of the twelfth postoperative day the level had returned almost to the control values The urinary excretion of corticoids continued to be elevated for eleven days following the operative procedure This prolonged elevation of corticoid excretion was to be ex-

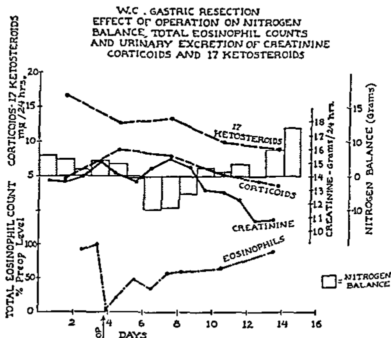


Figure 9 W C Gastric Resection, Effect of Operation on Nitrogen Balance, Total Eosinophil Counts and Urinary Excretion of Creatinine, Corticoids, and 17-ketosteroids Following the operation on the fourth day of the study there were five days of negative nitrogen balance, during which period the urinary excretion of corticoids was increased There was a gradual postoperative decline in the urinary excretion of 17-ketosteroids, a common finding following major operative procedures (see text) (Hardy, J D, Richardson, E M, and Dohan, F C *Surg, Gynec and Obst*, *96* 448, 1953, by permission of Surgery, Gynecology, and Obstetrics)

patient W. C Likewise, the emotional changes which the former experienced were less exaggerated than those of the latter

Measurements of the thyroid uptake of radioiodine in patient W C before and six days following operation indicated that thyroid activity was increased by the trauma

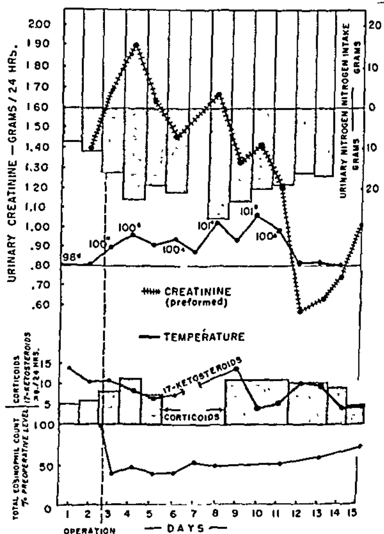
pected in view of the continued febrile course, and one might have anticipated that the total eosinophil count would remain at a low level for a longer interval. That it did not remain sharply depressed reflects, again, the fact that the eosinophil count may largely escape from the influence of the adrenal cortex in the later postoperative period in many individuals.

The preoperative control period on the standard diet was too short to permit a valid interpretation of the lean tissue metabolism, but it may be seen that operation caused a vigorous increase in the excretion of nitrogen. The urinary excretion of creatinine also increased following the operative procedure and gradually fell to

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Figure 10 D. C · Segmental Colon Resection, Total Eosinophil Counts, Maximum Oral Daily Temperature, and Urinary Excretion of Nitrogen, Creatinine, Corticoids, and 17-Ketosteroids The original operation which this patient had was not a particularly extensive one, but he developed an undiagnosed febrile complication in the postoperative period which resulted in a prolonged increase in the stress response The urinary excretion of corticoids did not return to preoperative levels until the fourteenth day of the study (the eleventh day following that in which the operation was performed). There was the usual gradual diminution in the excretion of 17-ketosteroids The prolonged depression of the total eosinophil count and the prolonged increase in corticoid excretion reflected his slow recovery In a general way, the variations in the urinary excretion of creatinine exhibited a direct correlation with the excretion of nitrogen. Moreover, the excretion of creatinine bore a direct relationship to the febrile episodes, being especially apparent in the marked fall in the excretion of creatinine as the temperature returned to normal on the twelfth day Our studies would appear to indicate that a simple segmental colon resection is a trauma of approximately the same magnitude as that of a gastric resection An abdominoperineal resection represents a more severe trauma than either of the previous operations (Hardy, J D, Richardson, E M, and Dohan, F C *Surg, Gynec and Obst., 96* 448, 1953 by permission of Surgery, Gynecology, and Obstetrics)


URINARY CREATININE — GRAMS / 24 HRS.
URINARY NITROGEN INTAKE GRAMS
URINARY NITROGEN GRAMS
CREATININE (preformed)
TEMPERATURE
17-KETOSTEROIDS
CORTICOIDS
TOTAL EOSINOPHIL COUNT % PREOPERATIVE LEVEL
CORTICOIDS 17-KETOSTEROIDS MG./24 HRS.
OPERATION
— DAYS —

after restoration of the blood pressure in oligemic shock by transfusion, and during the early convalescent period following a period of surgical stress was determined. The following conclusions were drawn: "(1) Operative trauma produces a marked increase in the output of 17-hydroxycorticoids in the adrenal venous blood of the dog over that seen in the convalescent animal. The secretion of ACTH from the pituitary in the convalescent animal is apparently intermittent and of a low order. (2) The adrenal cortex is capable of maintaining high levels of corticoid secretion in severe shock in spite of markedly reduced adrenal blood flow. When the mean blood pressure is reduced below 35 mm./Hg the adrenal blood flow may become so low that the minute corticoid output is reduced. The adrenal is still capable of responding to transfusion with an immediate increase in corticoid output, however (3) In some instances of hemorrhagic shock there is a marked increase in corticoid output above that seen with operative trauma alone This occurs just after the bleeding has been stopped, while the shock is still profound, and continues during the transfusion of the lost blood and in the immediate post-transfusion period The effect is usually gone within 15 minutes after the blood has been replaced This appears in part to be due to an increased ACTH release accompanying the shock, but there is some evidence to suggest that there may also be an increased adrenal response to ACTH under these circumstances This effect is not noted in the absence of ACTH" These workers found that in the dog the 17-hydrocorticosteroids in adrenal venous blood consisted largely of hydro-cortisone.

Such studies of the steroid content of adrenal venous blood hold much promise in solving problems related to adrenocortical activity in surgical trauma

quite low limits as the body temperature became normal and the general physiologic reaction began to subside The fever and other prolonged stress resulted in a characteristic decline in the excretion of 17-ketosteroids This patient too exhibited evidence of an increased thyroid activity following operation (radioiodine uptake)

Comment: The emotional and other phases of the clinical response to operation in this patient paralleled the changes depicted in Figure 10 (79) The cause of the febrile response, which exceeded that which one would ordinarily expect from the stress of operation per se, was not discovered

Blood Corticoid Levels

While the writer has had no personal experience with the measurement of blood corticoid levels during various forms of surgical trauma, a limited number of such data have become available This work is of such obvious importance in a review of adrenocortical function that a brief survey of some of the findings reported to date will be given

Representative of the studies of this facet of adrenocortical function in surgical stress are those of Hume and Nelson and of Steenburg (*Surgical Forum,* W. B. Saunders Company, Volume V, in press) and of Moncrief, Weichelbaum, and Elman (*Surgical Forum,* Volume IV, page 469)

Hume and Nelson conducted a series of ingenious acute and chronic experiments in dogs whose adrenal vein had been cannulated, by means of which the entire venous flow from the adrenal could be collected at will Thus it was possible to measure not only blood corticoid concentration but also adrenal blood flow The secretion of corticoids during operative trauma, in oligemic shock,

Final Comment

In concluding this discussion of the metabolic response to a single operation, the writer recommends that selected reports in the literature be consulted (80-95).

Moncrief and his associates measured the plasma concentrations of two groups of steroids of probable adrenocortical origin in normal subjects, in patients chronically ill, and in patients with malignancies. The levels in the last group were higher. After major operations the blood levels of both groups of steroids rose, but fell to normal in most cases in 24 hours. No rise occurred in patients undergoing relatively minor surgical trauma These investigators did not conclude that the postoperative increases in plasma levels of the two groups of steroids necessarily represented absolute increases in adrenocortical activity. The observed increases in plasma levels were considered to be due to one or more of the following: (a) a suppression of renal steroid excretion, (b) alterations in steroid metabolism by the liver, (c) a decreased rate of steroid uptake by the peripheral tissues, (d) an increased rate of steroid production by the adrenal cortex.

Finally, Steenburg also has described studies of the free 17-hydroxycorticoids in the peripheral blood of surgical patients before and following operation. Aware that the measurement of the urinary excretion of corticoids may not always reflect accurately alterations in adrenocortical activity (for example, the glomerular filtration rate may alter corticoid excretion and conjugation by the liver may change the form of the steroids), he found that during an operative procedure a rise in corticoid levels occurs which is considerably more rapid than that seen during maximal ACTH stimulation in the normal subject In some instances the increased blood corticoid levels subsided very quickly while in others the fall was gradual

The qualitative and quantitative study of blood corticoids in trauma is certain to provide a new chapter in surgical endocrinology

operation to be investigated. This operation affords an almost unique opportunity for the study in man of three equally spaced operations of approximately equal magnitude The patients were moved to private rooms and placed on a standard dietary intake (2500 calories and 150 grams of protein daily) for a control period of not less than one week preceding the operation At least three days prior to the operation complete urine collections were begun, and these collections were continued throughout the three stages of the operation and for several months thereafter. During the control period total eosinophil counts were performed, the patients were weighed, and the daily urinary excretion of creatine, creatinine, nitrogen, corticoids, and total neutral 17-ketosteroids was measured by the methods previously cited. The daily diets were calculated from foodstuffs available on the hospital menu, plus supplements, and the accuracy of these calculations was checked by random sampling The liquid portion of the diet was analyzed on ten different days and the solid portion on fifteen different days. The nitrogen intake, estimated to be 24 grams on the basis of the usual food values, was found on chemical analysis to average 22 9 grams, which was 4.6 per cent less than that calculated The average percentage deviation in the total diets analyzed was 7 8 per cent. During the first few days following operation intravenous alimentation was employed and consisted of Amigen or Travamin,* Travamin-alcohol, and glucose solutions On the day of operation all alimentation was by the intravenous route, but thereafter the usual procedure was to allow the patient to eat all that he could by mouth, and then to supplement this

*The Travamin and Travamin-alcohol mixtures used in these studies were donated by the Baxter Laboratories

Chapter III

THE PHYSIOLOGIC REACTION TO MULTIPLE STAGED OPERATIONS IN MAN

Introduction. It is often necessary to do certain operations in stages. This necessity may arise because of the magnitude of the trauma per se, or it may be due to the fact that the physiologic implications of doing the entire operation at one stage would be such as seriously to endanger a vital function, such as that of respiration were an entire standard thoracoplasty to be performed at one stage. The length of the interval between such operative stages has in the past been selected on a largely empiric basis. The patient's clinical course is followed daily and presently he appears able to withstand the next operation. The cellular mechanisms which result in his regaining an appearance which indicates to the examiner that he is ready to withstand the next operative stage are in large part unknown Yet, there must exist measurable physiologic processes whose levels of activity are altered following trauma, and whose return to preoperative levels signifies a return to health

The immediate objective of the following study was to examine the metabolic response to multiple staged operations in man, with the ultimate objective of formulating a more factual basis for the spacing of multiple procedures

Procedure and Methods

The three-stage thoracoplasty operation, performed for cavitary pulmonary tuberculosis, was selected as the first

operation to be investigated. This operation affords an almost unique opportunity for the study in man of three equally spaced operations of approximately equal magnitude. The patients were moved to private rooms and placed on a standard dietary intake (2500 calories and 150 grams of protein daily) for a control period of not less than one week preceding the operation. At least three days prior to the operation complete urine collections were begun, and these collections were continued throughout the three stages of the operation and for several months thereafter. During the control period total eosinophil counts were performed, the patients were weighed, and the daily urinary excretion of creatine, creatinine, nitrogen, corticoids, and total neutral 17-ketosteroids was measured by the methods previously cited. The daily diets were calculated from foodstuffs available on the hospital menu, plus supplements, and the accuracy of these calculations was checked by random sampling. The liquid portion of the diet was analyzed on ten different days and the solid portion on fifteen different days The nitrogen intake, estimated to be 24 grams on the basis of the usual food values, was found on chemical analysis to average 22.9 grams, which was 4 6 per cent less than that calculated. The average percentage deviation in the total diets analyzed was 7 8 per cent. During the first few days following operation intravenous alimentation was employed and consisted of Amigen or Travamin,* Travamin-alcohol, and glucose solutions On the day of operation all alimentation was by the intravenous route, but thereafter the usual procedure was to allow the patient to eat all that he could by mouth, and then to supplement this

*The Travamin and Travamin-alcohol mixtures used in these studies were donated by the Baxter Laboratories

intake in the evening with whatever intravenous alimentation was required to achieve the total intake of 2500 calories and 150 grams of protein.

Operations. All operations on the patients under study were performed by either the author or the Associate Investigator, Dr. Francis H. Cole, in order to preserve as much uniformity as possible. A general anesthetic was employed for all stages, but ether was usually used for the first stage and intravenous pentothal for the second and third stages Every effort was made to equalize the three stages, but the first stage of the posterolateral (Alexander) procedure remained the greatest. Blood loss was measured by weighing the discarded sponges and this loss was replaced as it occurred Approximately 12 patients were studied but, since the metabolic response to a particular type of thoracoplasty was similar in different patients, the results in only four of these subjects are presented here. In two patients (A.D and M.W) the standard posterolateral thoracoplasty was performed with the three stages spaced at three-week intervals In one patient (F. C) a multiple short incisional thoracoplasty (Wangensteen) was performed at weekly intervals and in one patient (R P) the multiple short incisional procedure was performed at three-week intervals In patient F C. the anterior stage was done first, but in patient R P. the anterior stage was done last.

Results*

Patient A D Three-Stage Posterolateral Thoracoplasty

Clinical Data This twenty-year-old man was admitted to The West Tennessee Tuberculosis Hospital with a diagnosis of far-advanced pulmonary tuberculosis, bi-

*Certain of these data have been presented elsewhere (96, 97)

lateral, chiefly on the left In the two months since he had known of his illness his weight had diminished from 158 pounds (72 kilograms) to 130 pounds (59 kilograms) Nevertheless, he did not appear to be acutely or chronically ill and the state of nutrition appeared to be fair. Roentgen examination revealed an extensive infiltration of the upper two-thirds of the left lung, and a 4 centimeter cavity was present just below the left clavicle. There was some infiltration in the left lower lobe, and a small amount of apical fibrosis was present in the right lung.

On bed rest and other conservative measures, including streptomycin and PAS (para-amino-salicylic acid),

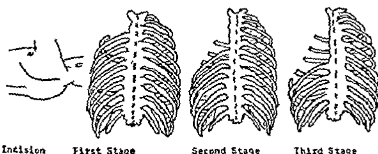


Figure 11 Three-Stage Posterolateral Thoracoplasty At the first stage the musculature is divided, as indicated by the incision, and two and one-half ribs are removed At the second and third stages a portion of the previous scar is divided as necessary for exposure, and additional ribs are resected as indicated

his general condition improved and the pulmonary infiltration cleared considerably However, one year later the cavity in the left upper lobe still remained open and a standard posterolateral thoracoplasty was performed (Figure 11) At the time of operation he was considered to be in good nutrition

intake in the evening with whatever intravenous alimentation was required to achieve the total intake of 2500 calories and 150 grams of protein.

Operations. All operations on the patients under study were performed by either the author or the Associate Investigator, Dr. Francis H. Cole, in order to preserve as much uniformity as possible. A general anesthetic was employed for all stages, but ether was usually used for the first stage and intravenous pentothal for the second and third stages. Every effort was made to equalize the three stages, but the first stage of the posterolateral (Alexander) procedure remained the greatest. Blood loss was measured by weighing the discarded sponges and this loss was replaced as it occurred. Approximately 12 patients were studied but, since the metabolic response to a particular type of thoracoplasty was similar in different patients, the results in only four of these subjects are presented here In two patients (A.D and M.W) the standard posterolateral thoracoplasty was performed with the three stages spaced at three-week intervals. In one patient (F C.) a multiple short incisional thoracoplasty (Wangensteen) was performed at weekly intervals and in one patient (R P) the multiple short incisional procedure was performed at three-week intervals. In patient F C. the anterior stage was done first, but in patient R P. the anterior stage was done last.

Results*

Patient A D. Three-Stage Posterolateral Thoracoplasty

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*Certain of these data have been presented elsewhere (96, 97)

did not. The most conspicuous trend noted in connection with the excretion of 17-ketosteroids was that the level gradually diminished during the course of the three operations, only to rise again almost to preoperative levels four weeks after the third and final stage. The excretion of corticoids remained generally above the original preoperative levels until almost one month following the third and final stage.

In Figure 13 are shown the nitrogen intake and the

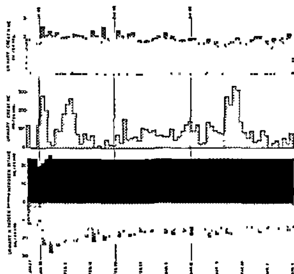


Figure 13 A D. Effect of Three-Stage Thoracoplasty on Nitrogen Metabolism There was a mild increase in the urinary excretion of creatinine following the first stage and, perhaps, following the second operative stage There was a definite increase in the urinary excretion of nitrogen for approximately ten days following the first operative procedure, but there was no marked effect of operation upon the excretion of nitrogen after the second and third procedures The first operative stage was the most extensive of the three

Laboratory Data: In Figure 12 it may be seen that the total eosinophil count fell promptly to zero after each of the three stages. The excretion of corticoids increased after each operation but the excretion of 17-ketosteroids

A.D.(♂) EFFECT OF THREE-STAGE THORACOPLASTY ON THE EOSINOPHIL COUNT AND URINARY EXCRETION OF CORTICOIDS AND 17-KETOSTEROIDS

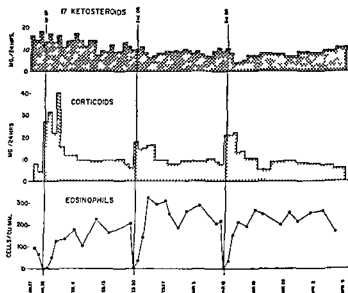


Figure 12 A D Effect of Three-Stage Thoracoplasty on the Eosinophil Count and Urinary Excretion of Corticoids and 17-Ketosteroids The urinary excretion of corticoids was substantially increased after each of the three operative stages, and this increase persisted in some degree for approximately three weeks The total eosinophil count fell to zero following each operative stage and then in each instance exhibited the usual rebound to levels considerably exceeding those present preoperatively The count did not stabilize until approximately three weeks to one month following the third stage The urinary excretion of 17-ketosteroids was not increased by the operations Instead, there was a gradual decline in the excretion of these steroid products, the lowest level being reached immediately following the third stage, after which there was a gradual increase in the excretion as convalescence progressed.

monary lesions Nevertheless, cavitation persisted in the left upper lobe, and a standard posterolateral thoracoplasty was performed to control the disease on the left side. At the time of operation she was considered to be in a good nutritional state.

Laboratory Data The excretion of steroids and the total eosinophil counts are presented in Figure 14 As with patient A D, the total eosinophil count did not begin to stabilize until almost three weeks following the third stage The urinary excretion of 17-ketosteroids was not strikingly affected by the individual operations, but this excretion did increase slightly at the time of the second operation There was a general downward trend over the span of the three operations, and this trend had not been reversed by the time the patient was dropped from the study approximately one month following the third and final stage. Had the patient been followed farther into convalescence, the level of 17-ketosteroid excretion would probably have risen again to the control levels The excretion of corticoids increased after each operation, and the level remained elevated for about twenty days after each stage It is of interest to note that the pronounced secondary rise in the excretion of corticoids which occurred on approximately March 17th (specimens for three days were pooled) was not associated with a significant fall in the total eosinophil count. We have commented previously on the relative lack of correlation between random elevations in the excretion of corticoids and in the total eosinophil count in the late postoperative periods.

In Figure 15 are shown the data for nitrogen metabolism and several interesting features are to be noted As this patient lost weight and, presumably, muscle mass there was a definite but gradual downward trend in the urinary excretion of creatinine This process had only begun to reverse itself when the study was discontinued

urinary excretion of nitrogen, creatinine and creatine. There was a moderate increase in creatinine excretion following each operation. Though the patient was in positive nitrogen balance prior to the first operation, there was a sharp increase in the urinary excretion of nitrogen following this procedure. The second and third operations had little immediate effect on the level of nitrogen excretion. (Fecal nitrogen analyses were not performed in this study.)

Comment· On the basis of these findings, it would appear that the first stage of a standard thoracoplasty represents a more severe and prolonged injury than gastric or colon resection Perhaps the trauma to bone which is involved is responsible for the prolonged duration of adrenocortical hyperfunction, since fractures are likely to be followed by a more prolonged increase in the urinary excretion of nitrogen than are soft tissue injuries. It is also of interest that a return of these measured variables to normal levels, approximately one month after the operation, was fairly well correlated with the return of the patient's good spirits and feeling of well-being

Patient M. W.· Three-Stage Posterolateral Thoracoplasty

Clinical Data This twenty-four-year-old woman was admitted to The West Tennessee Tuberculosis Hospital with a diagnosis of far-advanced pulmonary tuberculosis, bilateral, chiefly on the left Roentgen examination revealed moderate fibrotic and exudative streaking in the first and second interspaces on the right, with a few calcified nodules scattered throughout the lung parenchyma The left lung presented multiple cavities in the upper lobe, with fibrotic and exudative streaking involving most of the rest of this lobe and to a lesser extent the lower lobe. Her general physical condition responded gradually to streptomycin and other conservative measures, and this was accompanied by a regression of the pul-

M.W.(F) EFFECT OF THREE-STAGE THORACOPLASTY ON NITROGEN METABOLISM

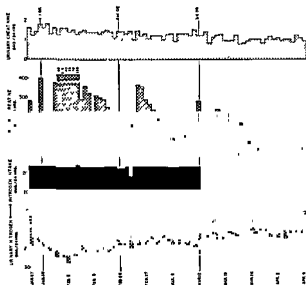


Figure 15 M W. Effect of Three-Stage Thoracoplasty on Nitrogen Metabolism The excretion of creatinine was not particularly affected by the individual operations, but there was a gradual decline in this excretion over the span of the three operative stages, indicating perhaps a decrease in the lean body tissue The pattern of creatine excretion was most interesting in that a spike in this excretion was associated with each operation, followed by a decline to relatively low levels, to be followed by a second rise approximately five to six days following the operation. The significance of this finding is not known, but it has been suggested that variations in creatine and creatinine excretion in the postoperative period may be related to alterations in thyroid activity The excretion of nitrogen was increased for approximately ten days following the first operation Following the second operation, however, there was little change in the excretion of nitrogen and following the third operation the patient was actually storing considerable amounts of this element.

MW(?) EFFECT OF THREE-STAGE THORACOPLASTY ON THE EOSINOPHIL COUNT AND URINARY EXCRETION OF CORTICOIDS AND 17-KETOSTEROIDS

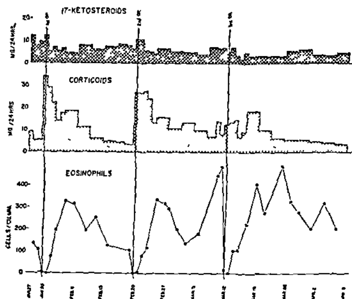


Figure 14 M W Effect of Three-Stage Thoracoplasty on the Eosinophil Count and Urinary Excretion of Corticoids and 17-Ketosteroids The individual operations had no consistent immediate effect on the urinary excretion of 17-ketosteroids, but there was a gradual decline in the level of excretion over the

was increased sharply after each operation, and this elevated

ing the third stage, the level of excretion of corticoids fell to low-normal levels The total eosinophil count fell promptly to zero after each operation and thereafter exhibited the usual rebound phenomenon It is of particular interest to note that the level of corticoid excretion was at times elevated during a sharp *increase* in the eosinophil count This is in accord with the fact that total eosinophil count may not bear an inverse relationship to corticoid excretion in the advanced postoperative period.

monary tuberculosis he was obviously critically ill and in a poor state of nutrition Roentgen examination revealed a soft pneumonic consolidation of the right upper lobe with a 5 or 6 centimeter cavity in this lobe. There was also scattered infiltration throughout the rest of this lung. The left lung presented soft infiltration in the mid-lung field with a moth-eaten appearance at the periphery He was placed on conservative therapy which

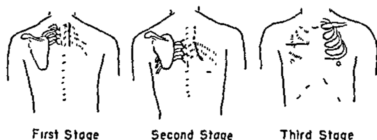


Figure 16 Multiple Short Incisional Thoracoplasty This shows a variant of the multiple short incisional thoracoplasty and was used in Patient R P The two posterior stages were done first and the anterior stage last

included streptomycin, PAS, and later INAH Eight months after admission a Monaldi drainage of the large upper lobe cavity was instituted, and one year after admission the "soft" disease in both lungs had cleared fairly satisfactorily and the cavity had diminished in size. A three-stage multiple short incisional thoracoplasty was performed with the two posterior stages being done first, followed by an anterior stage at which time the Monaldi tube was withdrawn (Figure 16) The patient was still in poor general physical condition and nutrition at the time of operation

approximately one month following the third stage. This was the only female studied, and it is of interest to compare her creatine excretion with that of the male patients Following each operation she exhibited first a brief rise in this excretion, then a marked fall, and on about the fifth postoperative day a sharp and rather prolonged secondary rise The significance of this pattern of excretion is problematical, but it is of interest in view of the impression that females react somewhat differently to the trauma of operation than do males. While most of the male patients exhibited some increase in creatine excretion at one time or another during the study, there was no consistent pattern of excretion, and it was not possible to correlate the variations in creatine excretion with variations in the other physiologic processes that were measured.

This patient exhibited a negative nitrogen balance for a brief period following the first operation Following the second operation there was no increase in the excretion of nitrogen, and following the third operation there occurred a definite retention of nitrogen Of course, the third stage of the posterolateral thoracoplasty is the least extensive and stressful of the three stages, and we have obtained evidence in patients subjected to other types of thoracoplasty that there is a tendency for the most extensive stage of the thoracoplasty to be followed by *the greatest excretion of nitrogen, though other* factors such as its sequence in the series have an influence

Question Do men and women react to the trauma of operation in a significantly different manner?

Patient R P *Multiple Short Incisional Thoracoplasty with Stages Spaced at Three-Week Intervals*

Clinical Data When this thirty-nine-year-old man was admitted to The West Tennessee Tuberculosis Hospital with the diagnosis of far-advanced bilateral pul-

debilitated from chronic disease. Even here, however, there was discernible a slight downward trend in the level of excretion of 17-ketosteroids following operation, particularly after the second and third stages Late in convalescence it appeared that the level of excretion of these substances might be increasing gradually, though the level was never within normal limits. The excretion of corticoids was low normal and the level was not sharply increased following operation. The fairly robust increase in the excretion of corticoids late in the postoperative period following the third operation was associated with fever.

The total eosinophil counts in this patient with very extensive tuberculosis were almost at zero from the time the study was begun Nevertheless, the count fell to absolute zero with the first operation and with each succeeding operation. The only time that normal levels were reached was during the period of rebound following the second stage. After the rebound following the third stage the count again declined to a low level which reflected the severe, chronic stress imposed by his disease

Comment: The findings in this patient are those which commonly prevail in the presence of a chronic debilitating illness Clinically this patient exhibited very little reaction to each of the stages of the thoracoplasty, but his physicians were not deceived into believing that the physiologic resources were such that he could absorb the operative trauma without seriously taxing his reserves. On the contrary, it was assumed that he simply was not able to exhibit a normal response to the operative trauma It is well known that the elderly patient may go through an operation "without turning a hair" and this mild clinical response to operation is usually in accord with the laboratory data, for these patients commonly show only a mild and brief increase in the urinary excretion of corticoids However, the fact that these pa-

Laboratory Data: In Figure 17 are shown the total eosinophil counts and the urinary excretion of corticoids and 17-ketosteroids. The preoperative excretion of 17-ketosteroids in this chronically and critically ill man was quite low, a characteristic finding in patients who are

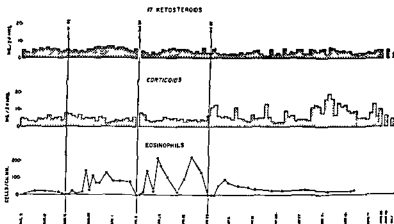


Figure 17 R P Effect of Three-Stage Thoracoplasty on the Eosinophil Count and the Urinary Excretion of Corticoids and 17-Ketosteroids The multiple short incisional method was used in this patient but, due to his extreme debility, the stages were spaced at three-week intervals instead of one week intervals. Indicative of the poor nutrition and chronic disease, the level of excretion of 17-ketosteroids was low prior to the first operation and this level never was within the normal range However, there was a slight gradual decline in the excretion of 17-ketosteroids, the lowest level being reached shortly following the third stage The excretion of corticoids was increased slightly following the first and second stages and somewhat more sharply following the third stage The total eosinophil count was consistently only slightly above zero before the first operation, but the count fell to absolute zero after each of the operative stages, the usual rebound phenomenon was noted. Following the rebound after the third stage the count gradually declined to the control values, which were quite low. This is the pattern of response which one frequently observes in chronically ill patients

he was again admitted to the hospital, and on streptomycin, PAS, and other conservative measures the bronchial fistula which had appeared on the right closed and the lung re-expanded. A cavity which had appeared in the left lung also closed Twelve months following the original admission the cavity in the right upper lobe had greatly diminished in size and a multiple short incisional thoracoplasty (Wangensteen), staged at one-week intervals, was performed on the right (Figure 18). He was well nourished at the time of operation.

Laboratory Data. The measurements of adrenocortical activity are presented in Figure 19. The level of 17-ketosteroid excretion diminished shortly after the first operation and remained low until several days following the third operation, after which it regained preoperative levels. There was a prompt increase in the excretion of corticoids after all operations. The total eosinophil count fell to zero following both the first and second operations, but did not fall entirely to zero after the third operation

The data for nitrogen metabolism are not given here, but it is of interest that this patient exhibited the greatest increase in nitrogen excretion following the second operative stage, which is the stage in this particular type of thoracoplasty which involves the division of the greatest amount of muscle.

Comment: These data illustrate that the patient can respond with a vigorous adrenocortical reaction to multiple operations spaced at one-week intervals The data further suggest that the thoracoplasty performed by the multiple short incisional method imposes less over-all stress upon the patient than does the three-stage posterolateral procedure Certainly the period of time over which the patient is being subjected to repeated instances of trauma is reduced from six weeks to two weeks

tients appear to be only mildly affected by the operation should not be viewed as a desirable circumstance, for clinical experience tells us that the operative mortality in depleted and in elderly patients is significantly greater than in young and healthy individuals.

Patient F. C.: Multiple Incisional Thoracoplasty Staged at One-Week Intervals

Clinical Data. This twenty-six-year-old man was admitted to The West Tennessee Tuberculosis Hospital with the diagnosis of bilateral far-advanced pulmonary tuberculosis Chest roentgen examination revealed a 3 centimeter cavity in the right upper lobe and some infiltration in the left mid-lung field. He soon left the hospital against medical advice and subsequently developed complications in the opposite lung. Several months later

Multiple Short Incisional Thoracoplasty

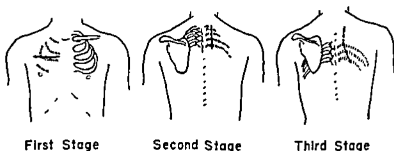


Figure 18 F C Multiple Short Incisional Thoracoplasty We have commonly performed the anterior stage first, followed by the posterior second and third stages The second stage usually represents the most extensive trauma of the three stages, since a greater mass of musculature is divided and since at the third stage one frequently uses a portion of the scar of the incision made at the second stage.

he was again admitted to the hospital, and on streptomycin, PAS, and other conservative measures the bronchial fistula which had appeared on the right closed and the lung re-expanded. A cavity which had appeared in the left lung also closed Twelve months following the original admission the cavity in the right upper lobe had greatly diminished in size and a multiple short incisional thoracoplasty (Wangensteen), staged at one-week intervals, was performed on the right (Figure 18). He was well nourished at the time of operation.

Laboratory Data. The measurements of adrenocortical activity are presented in Figure 19. The level of 17-ketosteroid excretion diminished shortly after the first operation and remained low until several days following the third operation, after which it regained preoperative levels. There was a prompt increase in the excretion of corticoids after all operations. The total eosinophil count fell to zero following both the first and second operations, but did not fall entirely to zero after the third operation.

The data for nitrogen metabolism are not given here, but it is of interest that this patient exhibited the greatest increase in nitrogen excretion following the second operative stage, which is the stage in this particular type of thoracoplasty which involves the division of the greatest amount of muscle.

Comment· These data illustrate that the patient can respond with a vigorous adrenocortical reaction to multiple operations spaced at one-week intervals. The data further suggest that the thoracoplasty performed by the multiple short incisional method imposes less over-all stress upon the patient than does the three-stage posterolateral procedure. Certainly the period of time over which the patient is being subjected to repeated instances of trauma is reduced from six weeks to two weeks.

F.C.(♂) EFFECT OF THREE-STAGE THORACOPLASTY ON THE EOSINOPHIL COUNT AND URINARY EXCRETION OF CORTICOIDS AND 17-KETOSTEROIDS

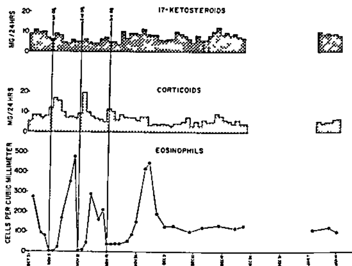


Figure 19 F. C. Effect of Three-Stage Thoracoplasty on the Eosinophil Count and Urinary Excretion of Corticoids and 17-Ketosteroids. It will be noted that the operations were staged at one-week intervals. Following each operation there was a sharp fall in the total eosinophil count, followed by the usual rebound. The urinary excretion of corticoids was increased after each operation. The urinary excretion of 17-ketosteroids was not conspicuously affected by the several individual operations, but there was a gradual decline in the level of this excretion, the lowest point being reached two days following the third stage. It is of interest that the pre-operative level of excretion of 17-ketosteroids was regained more promptly in this patient, whose three operations had covered an entire span of only two weeks, than was the case in the patients whose three operations covered a span of six weeks. It is clear that a patient is able to react vigorously to major operations staged at one-week intervals.

Concluding Comment

Adrenocortical Activity Following Staged Operations

Urinary Excretion of Corticoids The excretion of corticoids increased after all three operations in virtually all patients studied The magnitude of this increase appeared to be related to the state of health and nutrition of the patient. The subject whose general condition was the poorest (R P) exhibited a less marked response to the operations than did those whose state of nutrition had not seriously deteriorated. Nevertheless, there are definite exceptions to these findings for, as will be shown in Chapter V, we have studied patients in extremely poor physical condition and nutrition whose increase in corticoid excretion following operation was marked.

In Chapter II it was noted that following the increase in corticoid excretion in response to a single operation this excretion subsequently falls temporarily to low-normal levels It is clear from the present studies that this period of sub-average corticoid excretion may follow all of the three successive stages of thoracoplasty. The explanation for this finding is not settled This low level of excretion probably does not represent temporary exhaustion of the adrenal glands, for if a second operation is performed before the level of corticoid excretion has had an opportunity to fall the usual postoperative increase is again observed It is suggested that this low ebb of excretion may represent a purposeful attempt on the part of the body to reverse the alarm response, to allow retained fluid to be excreted, and to allow nitrogen retention to increase

Urinary Excretion of 17-ketosteroids. These studies of multiple operations indicate, as we have previously noted for single operations, that the level of excretion of 17-ketosteroids is not consistently elevated following surgical

operations. It is also apparent that the level of excretion of these steroid end-products diminishes in debilitated patients, as has been extensively documented by others in the past. The level falls gradually over the period during which the multiple operations are being performed, usually reaching its lowest level (in these experiments) several days following the final operative procedure. Variable periods of time are required for the excretion to rise again to control values, but in the majority of our patients this period was about one month. The level of excretion of 17-ketosteroids may prove to be useful as a yardstick of convalescence and as an index of the general state of health.

Total Eosinophil Counts. With but one minor exception, the total eosinophil count fell to zero following each operation and in all four patients this fall coincided with the postoperative increase in the levels of corticoid excretion. However, random secondary rises in corticoid excretion were not always accompanied by a fall in the total eosinophil count

In the patients who were chronically and critically ill, of whom R. P. is the only example presented here, the control eosinophil counts were near zero and the levels remained low throughout the period of study. This finding was considered indicative of the chronic stress imposed upon these patients by their far-advanced disease

The usual postoperative rebound to levels exceeding those obtained during the control period was observed after each operative stage in all patients. Following all stages the total eosinophil count required from fifteen to thirty days to stabilize at levels approximating those obtained preoperatively

Nitrogen Excretion Following Staged Operations

All patients who have been subjected to the standard posterolateral thoracoplasty have exhibited their maximum increase in nitrogen excretion following the first of the three stages. The two patients who underwent the multiple short incisional thoracoplasty at one-week intervals (one of whom is not reported here) exhibited at least as great an excretion of nitrogen after the second operation as after the first. This was also true of patient R. P., who underwent the multiple incisional procedure at three-week intervals. These findings are in accord with the extent of the surgery performed at the respective operative stages.

Practical Implications of These Studies

Patients who are operated upon only one week following a first operation are able to react vigorously to the second procedure. Therefore, necessary second operations, perhaps needed for the relief of postoperative intestinal obstruction, should not be delayed for fear that the patient cannot withstand the second procedure so soon

Normal levels of the measured physiologic activities were frequently not regained until from three to four weeks following the third and final stage Therefore, the patient who states that he does not feel able to return to work three weeks after a major operation may be stating a physiologic truth Actually, it is known that the normal physiology is altered for many months following a major operative procedure.

The level of 17-ketosteroid excretion may be useful as a yardstick for measuring the rate of convalescence and as an index of the general state of health While the excretion of 17-ketosteroids was not strikingly affected by

the individual operations, there tended to be a progressive decline in the excretion of these substances over the period of the three operative procedures. The excretion returned to preoperative levels only after from twenty to forty days following the third and final stage Therefore, while the adrenal cortex does respond vigorously to repeated trauma, as evidenced by alterations in the levels of corticoid excretion and the total eosinophil counts, the progressive decline in the excretion of 17-ketosteroids may indicate a selective depletion of this organ and presumably reflects a depletion of the patient's general reserve.

Chapter IV

ADRENOCORTICAL ACTIVITY FOLLOWING EXTENSIVE THERMAL BURNS IN MAN

THE ADRENOCORTICAL RESPONSE which follows extensive burns is one of the most intense that we have studied in our laboratory. Approximately 400 measurements of the twenty-four hour urinary excretion of corticoids and of 17-ketosteroids have been performed in duplicate in fifteen burn patients, and frequent total eosinophil counts have been made The results of the study of four representative patients will be presented.

Results

Patient L. O.: 22 Per Cent Scald Burn

Clinical Data This twenty-eight-year-old man was burned when an assailant poured a pot of hot grease over his back, shoulders, and upper arms. The burned areas were limited chiefly to the posterior or extensor surfaces, and it was possible to treat him by the open or exposure method Fluid requirements were not excessive, serious infection did not develop, and the catabolic response was not great The crust thinned and separated from his back in two large sheets on the twenty-second day and it was found that, contrary to the original opinion, no grafting was necessary.

Laboratory Data The values for the urinary excretion of corticoids and 17-ketosteroids and the total eosinophil counts are presented in Figure 20. The urinary ex-

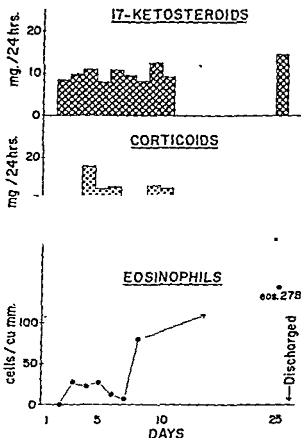


Figure 20 L O 22 Per Cent Scald Burn Total Eosinophil Counts, and Urinary Corticoids and 17-Ketosteroids The level of excretion of 17-ketosteroids in this patient was within normal limits and was never depressed, indicating that the injury was not sufficiently severe to be a debilitating one The urinary excretion of corticoids was increased, but this increase was not great The total eosinophil count was at zero on admission but promptly rose and this, as much as anything else, indicated the superficial nature of his burn Grafting was not required

cretion of 17-ketosteroids was slightly depressed in this male patient during the early stage of the burn, but by the time he was discharged the single late measurement performed indicated that the level was within the normal limits for men. The excretion of corticoids remained at essentially normal levels during the first twenty-four-hour period but thereafter rose to levels which were considerably elevated. It is of interest that at the time of discharge on the twenty-fifth day, when the total eosinophil count was 278 cells per cubic millimeter, the excretion of corticoids was still elevated. The total eosinophil count was zero at the time the patient was admitted but during the next twenty-four hours the level rose and never again reached a level as low as that obtained on admission.

Comment. The burn injury in this patient was one of only moderate extent and severity, and this circumstance was reflected by the relatively mild alarm response. This was evidenced by the moderate rise in the excretion of corticoids, by the fact that the extent and chronicity of the burn was not sufficient to bring about a lowering of the excretion of 17-ketosteroids, and by the fact that the total eosinophil count remained at zero for only a brief interval.

Patient G. S.: 35 Per Cent Flame Burn

Clinical Data. This fifty-nine-year-old man sustained flame burns of the anterior surface of the body, including the upper abdomen, chest, right arm and hand, and left hand when he had an epileptic seizure while smoking in bed. Approximately one-half of the burn was considered to be of third degree. He was treated by the open method with the exception of the hands and arms, which were dressed, and fluid therapy was instituted according to established procedure. The urinary sodium output remained low until the sixth day, at which time the body

weight curve reached its peak. Thereafter the urinary sodium excretion remained at fairly high levels until the eleventh day, when it began to decline This decline was associated with a concomitant reversal of the previous decrease in weight to a gain in weight, and the weight curve did not fall to admission levels until the twentieth day. He became slightly dyspneic on the sixth hospital day and these symptoms increased in severity over the next two days. A chest roentgenogram showed "congestive changes" and he was digitalized on the eighth day, shortly thereafter the dyspnea subsided. Skin grafting was carried out on the thirty-fourth and the fifty-third days

Laboratory Data In Figure 21 it may be observed that the level of 17-ketosteroid excretion in this patient was well maintained until the additional stress of grafting was imposed on the thirty-fourth day, following which the level of 17-ketosteroid excretion rapidly declined The excretion of corticoids remained rather sharply elevated throughout most of the hospital stay and was still somewhat elevated when he was discharged 80 days following the injury Only twice was the total eosinophil count at zero, and we have come to believe that a prompt rise in the count is a favorable prognostic sign The slight fluctuations which were observed were usually associated with the changing of the dressings

Comment The injury in this patient was more extensive than that in the previous patient, though only a relatively small portion of the injury finally required grafting That the trauma was well tolerated was evidenced by the fact that the level of urinary 17-ketosteroids was well maintained for many days and did not fall until the additional stress of skin grafting was imposed

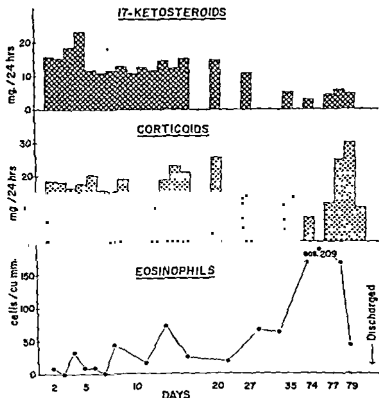


Figure 21 G S 35 Per Cent Flame Burn Total Eosinophil Counts, and Urinary Corticoids and 17-Ketosteroids The level of 17-ketosteroid excretion was well maintained until the late post-burn period when skin grafting furnished the additional burden that was required to cause a decline in the excretion of these products The urinary excretion of corticoids was increased over a long period of time and, indeed, was not normal even at the time of discharge The total eosinophil count was depressed for a considerable period of time This man had a moderately extensive deep burn which required skin grafting

weight curve reached its peak. Thereafter the urinary sodium excretion remained at fairly high levels until the eleventh day, when it began to decline. This decline was associated with a concomitant reversal of the previous decrease in weight to a gain in weight, and the weight curve did not fall to admission levels until the twentieth day. He became slightly dyspneic on the sixth hospital day and these symptoms increased in severity over the next two days. A chest roentgenogram showed "congestive changes" and he was digitalized on the eighth day, shortly thereafter the dyspnea subsided. Skin grafting was carried out on the thirty-fourth and the fifty-third days.

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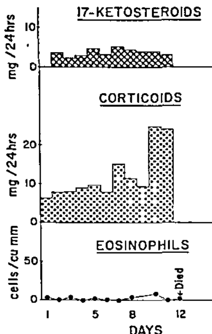


Figure 23 A Ni 40 Per Cent Flame Burn Total Eosinophil Counts, and Urinary Corticoids and 17-Ketosteroids This patient sustained a severe injury The level of excretion of 17-ketosteroids was always at a subnormal level There was an increase in the urinary excretion of corticoids which was particularly striking on the two days prior to her death The fact that the total eosinophil count remained at zero for the duration of the illness was considered to indicate a grave prognosis

Patient A. Ni.: 40 Per Cent Flame Burn

Clinical Data: This forty-seven-year-old woman was burned on the anterior surface of the thorax, face, and neck when a cigarette ignited the illegal "explosive sweater" which she was wearing (Figure 22). Both arms and hands were burned, and at least 30 per cent of the total burn was considered to be full thickness third degree injury with charring. The hands and arms were

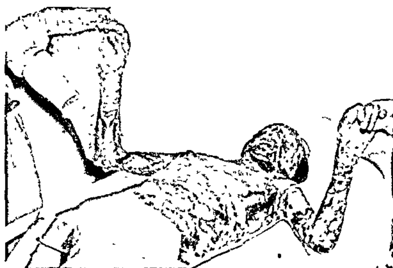


Figure 22 A Ni 40 Per Cent Flame Burn

dressed but otherwise the patient was treated by the open method.

She did poorly from the beginning, and the urinary output was never completely satisfactory Little sodium was excreted in the urine and a diuresis of this ion never occurred. On the twelfth day after injury the serum electrolyte levels were normal She died suddenly that night.

Laboratory Data In Figure 23 it may be seen that

biotic therapy. He would not eat and efforts to feed him by tube resulted, repeatedly, in marked distention and diarrhea, regardless of the numerous variations in the composition of the feeding mixture. His was a progressively downhill course.

Laboratory Data: This patient exhibited (Figure 24) what would appear to have been a maximal adrenocortical response to the injury. The level of excretion of 17-ketosteroids declined gradually over the course of the thirty-nine days that he lived, but the urinary outpouring of corticoids was abundant from the time of admission up to and including the twenty-four-hour period which preceded that in which he died. This finding is in accord with those which we have seen in other patients who have died, namely, that while the level of 17-ketosteroid excretion declines in a chronic illness, the excretion of life-supporting corticoids is generally maintained at a normal or elevated level during the stress which precedes death.

With few exceptions the total eosinophil count remained at zero from the time of admission to the time he died, and in the light of the knowledge that we have gained from these studies of burn patients, we view an eosinophil count of this type as indicative of a poor prognosis.

Comment: This patient exhibited a prolonged and intense adrenocortical response to his injury. At no time did it appear advisable to attempt to skin graft the wounds, there being always the hope that his critical condition would improve. It should have been possible to feed him more successfully, and it will surely become possible better to control the infection which looms so large as a factor in the so-called stage of toxemia which is associated with extensive burns.

the level of 17-ketosteroid excretion in this patient was quite low from the time of admission to the time of death. One possible cause of this finding was that the patient was in a state of malnutrition at the time she was burned An additional factor may have been the fact that the attending physician elected to treat this patient with 100 milligrams of cortisone daily from the time of admission through the fourth day of hospitalization. It is well known that the administration of cortisone to certain individuals will suppress the urinary excretion of 17-ketosteroids (Chapter VI) However, it is unlikely that the cortisone therapy was the sole cause of the low 17-ketosteroid excretion observed here.

The excretion of corticoids rose rather slowly but was at a markedly elevated level during the last two twenty-four-hour periods preceding death.

The total eosinophil counts gave a clue to the true extent of this injury A total eosinophil count of zero persisted from the time of admission to death. This type of curve is rather characteristic of that found in extensive full-thickness injury

Comment. This patient exhibited an extreme adrenocortical response to an extensive and fatal burn.

Patient R. J. 55 Per Cent Flame Burn

Clinical Data This twenty-seven-year-old male truck driver was burned when gasoline fumes exploded and burned his house down He sustained severe third degree burns of the back, hands, and both legs In addition, there were second degree burns of the face and neck On admission he was disoriented and, though at times the sensorium improved, he never fully regained his faculties during the thirty-nine days that he survived Since his critical clinical condition never improved to an extent that would permit skin grafting, he developed an extensive wound infection, which was refractory to anti-

Summarizing Comment

Eosinophil Counts

The findings which have been presented are in accord with those reported by Evans and Butterfield (98), and by Wight and her associates (99). The former workers found that the depression in the eosinophil count appeared to be closely related to the extent of the burn injury and was almost complete in 40 to 60 per cent burns They found that the natural stress response of the severely burned patient was surprisingly large, as assessed by measurements such as we have used, and with this impression we would surely agree It would appear that a prolonged severe depression of the total eosinophil count following *the initial injury indicates a poor prognosis*

Corticoid Excretion

The excretion of corticoids is elevated following a burn of significance, and this excretion remains at either an elevated or normal level throughout the course of the injury, regardless of whether the patient eventually dies or recovers.

We would agree with Wight and her associates that there is no correlation between adrenal response and the extent of the burn except in minor injuries Both moderate and severe burns respond in a similar fashion in regard to the excretion of corticoids and, though perhaps to a lesser extent, to the changes in the total eosinophil count

17-ketosteroid Excretion

While there may be a brief increase in the excretion of 17-ketosteroids following a burn, the most characteristic finding in severe injuries is that of a gradual decline.

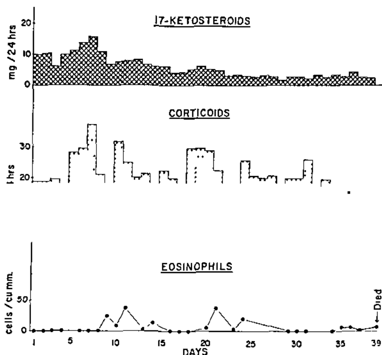


Figure 24 R J 55 Per Cent Flame Burn Total Eosinophil Counts, and Urinary Corticoids and 17-ketosteroids The excretion of 17-ketosteroids exhibited the usual gradual decline to low levels as the extensive injury became chronic Had the patient recovered, the 17-ketosteroid excretion would have returned to normal levels late in convalescence The excretion of corticoids remained elevated until he died, and we have observed that the excretion of corticoids usually remains at normal or elevated levels up to the time of death, if shock and oliguria are absent The total eosinophil count remained at or near zero for the entire thirty-nine days that he lived, again indicating the very severe nature of the injury and the unfavorable prognosis

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The excretion of corticoids is elevated following a burn of significance, and this excretion remains at either an elevated or normal level throughout the course of the injury, regardless of whether the patient eventually dies or recovers

We would agree with Wight and her associates that there is no correlation between adrenal response and the extent of the burn except in minor injuries. Both moderate and severe burns respond in a similar fashion in regard to the excretion of corticoids and, though perhaps to a lesser extent, to the changes in the total eosinophil count

17-ketosteroid Excretion

While there may be a brief increase in the excretion of 17-ketosteroids following a burn, the most characteristic finding in severe injuries is that of a gradual decline.

Furthermore, the extent of this decline reflects in a general way the magnitude of the injury, for in the relatively mild burn a normal level of 17-ketosteroid excretion may be maintained.

Chapter V

ADRENOCORTICAL FUNCTION IN MALNOURISHED CANCER PATIENTS, WITH OBSERVATIONS ON THE RELATIVE DEPENDABILITY OF THE ACTH-EOSINOPHIL TEST AND THE EPINEPHRINE-EOSINOPHIL TEST AS MEASURES OF ADRENOCORTICAL RESERVE

THE PURPOSE of these investigations was to determine whether or not adrenocortical activity in malnourished patients with gastrointestinal cancer is quantitatively impaired Eleven patients were studied who had lost from 7 to 20 kilograms in body weight, the average being approximately 12 kilograms (26 lbs.). The twenty-four-hour excretion of corticoids and of 17-ketosteroids was measured, and the adrenocortical reserve was estimated by means of the intramuscular epinephrine-eosinophil test and the ACTH-eosinophil test In a second group of 19 patients the ACTH was infused intravenously.

Results

The clinical data for the first group are presented in Table I, and the measurements of adrenocortical function are presented in Figure 25

Urinary Corticoid Excretion

In only one patient (M L) was the corticoid excretion subnormal In three patients the corticoid excretion was

TABLE 1

PATIENTS STUDIED

Name	*Age*	*Sex*	*Diagnosis*	*Weight Kilograms*	*Approximate Weight Loss Kilograms*
R B	50	F	Carcinoma of the stomach	49	9
F B.	50	F	Carcinoma of sigmoid colon	41	7
M L.	51	F	Carcinoma of the colon	50	7
P. H	60	F	Carcinoma of the head of pancreas		18
D. R	62	M	Carcinoma of the esophagus	47	14
G M	53	F	Carcinoma of the esophagus	35	16
C P	53	M	Carcinoma of the stomach	41	20
M F	51	M	Carcinoma of the stomach	51	12
F N	76	M	Carcinoma of the esophagus	63	18
L M	52	M	Carcinoma of the stomach	50	18
W C	49	M	Carcinoma of rectum with metastases	47	19

definitely greater than normal (C P., M. F., and F. N) There was no definite correlation between the level of corticoid excretion and the amount of weight loss, and this is in accord with the fact that a normal level of corticoid excretion is usually maintained in chronic disease states. Moreover, in patients who have sustained extensive burns the level of corticoid excretion remains normal or elevated up to the time of death These findings are not surprising, for an adequate supply of corticoids is essential for life.

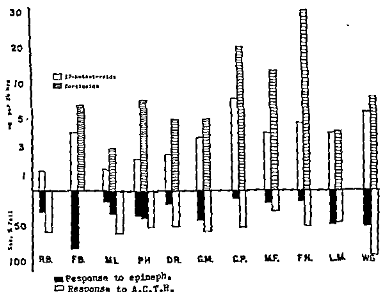


Figure 25 Malnourished Cancer Patients. Urinary Excretion of Corticoids and 17-ketosteroids and the Response of the Total Eosinophil Count to Intramuscular Injections of Epinephrine and of ACTH All ten patients so studied exhibited a normal or elevated excretion of corticoids This is in accord with the fact that debilitated or seriously ill patients do usually show a normal or elevated level of corticoid excretion, in contradistinction to the excretion of 17-ketosteroids, which is usually depressed Only one of the ten patients had an excretion of 17-ketosteroids which was within normal limits, the others being subnormal Injection of 0 3 milligrams of epinephrine intramuscularly produced a fall in the total eosinophil count of more than 50 per cent in only one of the ten patients so studied The injection of 25 milligrams of ACTH produced at least a 50 per cent fall in all but two subjects. It is concluded that the epinephrine-eosinophil test is unreliable as an indicator of the functional reserve of the pituitary-adrenocortical axis (Wilson, F. C, Jr, and Hardy, J. D, *Federation Proc*, 12, 1953)

Urinary 17-ketosteroid Excretion

In marked contrast to the urinary excretion of corticoids, the excretion of 17-ketosteroids was normal in only one patient (C. P.) (who incidentally had lost 45 pounds) and even here the excretion was at the lower limit of normal The remaining patients studied had excretions which ranged from 1.4 to 4 8 milligrams per 24 hours The normal range of values in our laboratory is approximately 7 to 20 milligrams for males and 6 to 15 milligrams for females.

ACTH-Eosinophil Tests

Total eosinophil counts were done before and four hours following the intramuscular injection of 25 milligrams of ACTH With the exception of two patients (M. F. and L. M.), each of whom had an inoperable carcinoma of the stomach, the total eosinophil count in all patients fell to 50 per cent or less of the preinjection level by the end of four hours, indicating an apparently normal reserve of cortical activity.

Epinephrine-Eosinophil Tests

The total eosinophil count was measured before and four hours following the intramuscular injection of 0 3 milligrams of epinephrine With the exception of one patient (F D.) the fall in circulating eosinophils was less than 50 per cent Although these findings could be interpreted as indicating that the patients had a reduced pituitary-adrenal function, the more reliable tests indicated that adrenocortical function was adequate.

Intravenous ACTH Test

In a further study of the adrenocortical reserve in debilitated surgical patients, Jabbour and Hardy (*Surgical*

Forum, Volume V. W. B Saunders Company, in press) used the intravenous ACTH test (30) in five apparently normal subjects awaiting elective herniorrhaphy and fourteen markedly debilitated individuals most of whom had advanced malignancy. In one sixty-eight-year-old "normal" and in one of the chronically ill subjects there was no increase in the urinary excretion of either corticoids or 17-ketosteroids, presumably indicative of a diminished adrenocortical responsiveness. However, both of these subjects had total eosinophil counts that were almost at zero during the control period (indicating at least a degree of adrenocortical activity) and both withstood operation without event. A third subject, whose response to operation only was measured, exhibited no increase in the excretion of either corticoids or 17-ketosteroids Yet, the eosinophil count fell to zero and he underwent the operation without difficulty Thus, the total eosinophil count emerges as a useful test, being apparently a more sensitive indicator of increases in adrenocortical activity than is the excretion of corticoids or 17-ketosteroids. Of course, other factors than alterations in adrenocortical activity may influence the total eosinophil count

It was concluded that, while a diminished adrenocortical response may be observed not uncommonly in chronically ill subjects, it must be rare that these subjects cannot survive surgery without hormonal replacement therapy.

General Discussion of Results

The steroid excretion data presented here for cancer patients, most of whom were at middle age or older, are not in disagreement with the data for the excretion of corticoids and 17-ketosteroids in senile men and women reported by Heller and Shipley (100). While the level

of 17-ketosteroid excretion is usually diminished in the aged and in states of malnutrition and other chronic disease, the excretion of corticoids is well maintained except where disease involves the adrenal cortex itself.

The results which we have obtained concerning the eosinophil response to the intramuscular injection of epinephrine indicate a poor correlation between the fall in the eosinophil count and the functional reserve of the adrenal cortex, if this reserve is accurately reflected in the urinary excretion of steroids. Patients with a high level of corticoid excretion frequently showed less response to epinephrine than did those with low corticoid excretion. Though the number of patients studied here was small, it appears reasonable to suspect that the epinephrine-eosinophil test is of little value in estimating adrenocortical reserve, and this suspicion is strengthened by an increasing number of reports in the literature (7, 8, 9, 101) In marked contrast, the ACTH-eosinophil test appears to be a rather reliable measure of the functional reserve of the adrenal cortex, particularly if the ACTH is administered intravenously.

Chapter VI

ADRENOCORTICAL HYPERPLASIA: CASE REPORT WITH PHYSIOLOGIC STUDIES*

THE FOLLOWING CASE study serves to introduce the general subject of adrenocortical hyperplasia, and it emphasizes certain of the problems which may render the management of this condition difficult

History and Physical Examination

The patient was a fourteen-year-old schoolgirl who consulted Dr. Hall S. Tacket with the chief complaint of "nervous spells." Physical examination revealed a husky voice, a receding (scalp) hairline, masculine facial features, absence of breast development, amenorrhea, male pubic hair escutcheon, purplish striae of the thighs, a stocky build, and a clitoris which was approximately 3 centimeters x 1.5 centimeters A vagina was present. Her mother stated that the clitoris had been enlarging for approximately six years. The patient did not have hypertension, and the glucose tolerance curve and plasma electrolytes were within normal limits

From these findings it appeared likely that the correct diagnosis was that of adrenocortical hyperplasia producing the adrenogenital syndrome, since the long duration of the physical changes made the presence of tumor unlikely. Preliminary steroid measurements (Figures

*This patient has been studied in collaboration with Dr Hall S Tacket and the long-range clinical results will be reported at a later date.

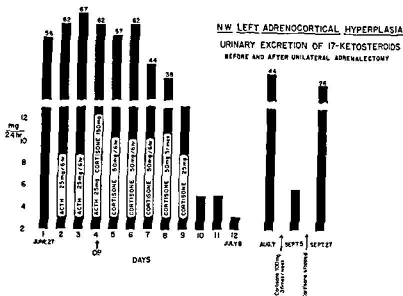


Figure 26 N C. W Left Adrenocortical Hyperplasia, Urinary Excretion of 17-ketosteroids before and after Unilateral Adrenalectomy. Before operation the administration of 25 milligrams of ACTH intramuscularly every six hours produced a rise in the 17-ketosteroid excretion from 56 milligrams to 67 milligrams Following operation there was a gradual fall in the level of 17-ketosteroid excretion to a normal level on the sixth day following that on which the operation was performed This gradual fall in the level of excretion probably reflects the reaction of the remaining normal adrenal to the stimulus of operation After the analysis of August seventh revealed that hypertrophy of the remaining adrenal gland had occurred and produced a level of excretion of 17-ketosteroids of 44 milligrams pe [illegible] was a drop to a level of [illegible] Cortisone was then st [illegible] in the excretion of 17-ketosteroids Cortisone therapy was then reinstituted and has since been given continuously but in gradually decreasing doses until, at the time of writing, she is receiving 25 milligrams four times weekly and a normal level of 17-ketosteroid excretion has been maintained The adrenogenital syndrome has been replaced by partial feminization and with menstruation

26 and 27) showed that the urinary excretion of not only the 17-ketosteroids (largely from androgens) but also the corticoids (largely from 11-oxysteroids) was elevated. That the excretion of corticoids was increased was not surprising in view of the purplish striae of the thighs, a feature of Cushing's syndrome However, the increase in the secretion of 11-oxysteroids, excreted as corticoids, was not nearly so great as was the increase in the secretion of androgens, excreted as 17-ketosteroids and which had produced the adrenogenital syndrome with masculinization.

Operation

Under general anesthesia an operation was performed through a transverse upper abdominal incision. The ovaries were palpated for and both were present, though small The uterus was infantile. Both adrenals were palpated and the right adrenal seemed to be normal in size. The left adrenal was definitely enlarged. The incision was therefore extended into the left subcostal region, and the left adrenal was exposed by retracting the stomach upward and the tail of the pancreas downward. Though its normal shape had been preserved, this adrenal appeared to be from two to three times normal size and upon removal weighed 19 (average normal, approximately 9) grams after the fat had been cut away by the pathologist (Figure 28)

The transverse incision was then extended farther into the right flank, and the right adrenal was completely exposed and carefully inspected It was normal or slightly less than normal in size and, though the operator was aware that this adrenal might in turn hypertrophy, it was decided not to resect any of the right adrenal at that time.

During and following operation the patient received the therapy noted in Figures 26 and 27 The postop-

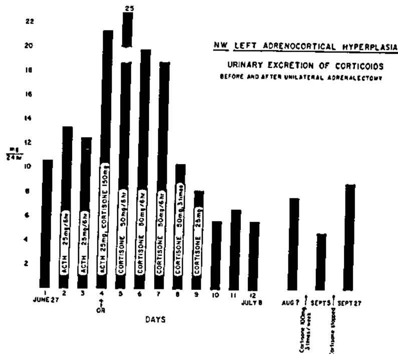


Figure 27 N C W Left Adrenocortical Hyperplasia, Urinary Excretion of Corticoids before and after Unilateral Adrenalectomy The administration of ACTH in a dosage of 25 milligrams intramuscularly every six hours resulted in a rise in the urinary excretion of corticoids from 11 to approximately 13 milligrams before operation However, the stimulus of 100 milligrams of ACTH per twenty-four hours was not nearly so great as that produced by the operation, since during the day in which operation was performed the excretion of corticoids rose to 21 milligrams—and this with only one adrenal remaining Instead of a precipitous fall in the urinary steroid ex-

atrophy often present in the adrenal opposite a functioning tumor

cretion after the administration of cortisone was stopped We have found that the administration of 50 milligrams of cortisone every six hours may not increase urinary steroid excretion (see ref., p 113)

erative course was essentially uneventful though she did have a moderate amount of fever, as patients frequently do following the resection of a significant fraction of the functioning adrenocortical tissue.

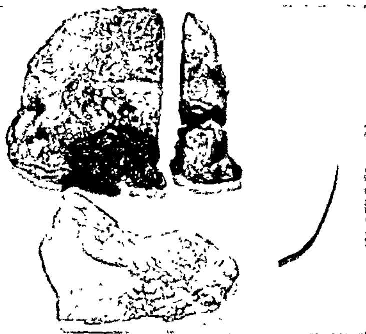


Figure 28 N C W *Adrenocortical Hyperplasia causing Adrenogenital Syndrome* Above is shown the excised left adrenal gland and below is shown a normal adrenal gland obtained from another patient at autopsy for comparison At the right is shown a piece of [illegible]

[illegible]

Measurements of Urinary Corticoids and 17-ketosteroids

Steroid Measurements on Admission

The steroid excretion data are presented in Figures 26 and 27. At the time of admission the twenty-four-hour urinary excretion of corticoids was found to be 12 milligrams and 11 milligrams on two separate occasions (normal for laboratory, 5 to 8 milligrams). The twenty-four-hour excretion of 17-ketosteroids was, however, 60 milligrams and 56 milligrams on two separate occasions (normal for women, 6 to 14 milligrams per twenty-four hours). Thus, the preliminary steroid excretion data were in accord with the physical findings in this patient: The preponderant increase in the elaboration of androgenic compounds excreted as 17-ketosteroids had produced features of the adrenogenital syndrome, in contradistinction to the features of Cushing's syndrome which are usually produced by a preponderant increase in the elaboration of corticoids These syndromes frequently overlap, and at least one feature of Cushing's syndrome was present in this patient (striae).

Effect of ACTH on Steroid Excretion Preoperatively Following the intramuscular administration of 25 milligrams of ACTH each six hours, the urinary excretion of 17-ketosteroids increased from 56 to 67 milligrams and the corticoid excretion increased from 11 milligrams to 13 milligrams, per 24 hours Furthermore, while the administration of ACTH did effect some increase in the excretion of these steroids, it was not surprising that this amount of ACTH failed to effect a marked increase in the presence of adrenocortical hyperplasia (as, we shall see in Chapter VII, it did in the presence of a tumor). The amount of exogenous ACTH administered may have been relatively small in the presence of the increased amount of endogenous ACTH which has been demon-

strated in the blood of patients with adrenocortical hyperplasia (23).

Response of the Remaining (Normal) Adrenal to Resection of the Hypertrophied Adrenal

Following resection of the hyperplastic left adrenal, the normal right adrenal responded vigorously to the marked stimulus of the operation Whereas the administration of ACTH preoperatively had increased the twenty-four-hour excretion of corticoids only from 11 milligrams to 13 milligrams — and this with the hyperplastic adrenal still *in situ* — the much greater stimulus of the operation increased the corticoid excretion from 12 milligrams to 25 milligrams The high preoperative level of 17-ketosteroid excretion persisted for two twenty-four-hour periods following that in which the operation was performed and then gradually subsided, reaching a normal level of 5 milligrams per 24 hours on the sixth day In contrast, studies presented in the next chapter will show that following the removal of a functioning tumor (the adrenal opposite which is usually atrophied) approximately twenty-four to forty-eight hours were required for the utilization or excretion of the large amounts of steroids deposited in the tissues in hyperadrenocorticism The adrenal opposite unilateral adrenocortical hyperplasia is usually not atrophied.

Steroid Excretion in the Immediate and Late Postoperative Periods and in the Succeeding Months

In the immediate postoperative period the urinary excretion of corticoids and 17-ketosteroids fell to normal levels (Figures 26 and 27) Nevertheless, the patient's parents were advised that the other adrenal might become hyperplastic and that, in this event, the girl would be treated with cortisone, which had been shown by Wilkins and his associates (102) to diminish androgen pro-

duction. Five weeks following operation the twenty-four-hour excretion of 17-ketosteroids had again risen sharply, indicating that the remaining adrenal gland had now become hyperplastic. Cortisone therapy was begun on a schedule of 100 milligrams three times weekly by intramuscular injection, and, as may be seen in Figure 28, this was effective in reducing the excretion of 17-ketosteroids At this point the cortisone therapy was stopped temporarily, and after two weeks the excretion of 17-ketosteroids had risen again. Cortisone was resumed and since then the patient has been maintained on gradually diminishing doses of cortisone until at the present writing she receives 25 milligrams four times a week The suppression of the 17-ketosteroid excretion has now been effectively maintained for a period of 18 months, and feminization is well advanced The breasts have developed, female contours have appeared, body hair distribution (including that of the scalp) has assumed a more feminine pattern, and menstruation has been established *

*Since the manuscript was written it has become progressively more difficult to suppress androgen production with oral cortisone therapy, and feminization has regressed

Chapter VII

MASCULINIZING ADRENOCORTICAL CARCINOMA: CASE REPORT WITH PHYSIOLOGIC STUDIES

THE PHYSICAL, physiologic, and chemical changes produced by functioning tumors of the adrenal cortex are of importance not only because of the unusual clinical interest attending these conditions, but also because of the light which the study of patients with such tumors sheds upon the more general aspects of adrenocortical physiology In the study of a patient with a masculinizing adrenocortical carcinoma we have sought answers to the following questions (1) What is the relative preponderance of urinary 17-ketosteroids over urinary corticoids in a patient whose masculinizing tumor has produced the adrenogenital syndrome? (2) Does the preoperative administration of ACTH increase the secretory activity of an adrenocortical carcinoma? (3) What interval of time is required to clear the body tissues of the excessive deposits of steroids, following resection of the tumor? (4) Does the administration of exogenous ACTH result in the suppression of the elaboration of endogenous ACTH by the patient's own pituitary? (5) Are steroid excretion studies of value in the subsequent management of a patient whose functioning carcinoma has been resected?

States of adrenocortical hyperfunction still present many therapeutic problems, and thus it is important that all feasible laboratory data be gathered from patients with such disorders



Figure 29 Roentgen Studies, Large Right Adrenocortical Tumor *Upper Left* Roentgen examination of the chest and diaphragm showing elevation of right diaphragm with slight displacement of the heart to the left *Upper Right* Intravenous pyelogram showing depression of the right kidney *Lower Left* Cholecystogram showing displacement of the gallbladder into the left upper quadrant *Lower* [illegible]

R. S., and Bowerman, E. P. *Am Surgeon, 19* 835, 1953.)

History and Physical Examination*

The patient was a slender twenty-six-year-old married woman employed as a medical secretary. She had been well until approximately two years before admission when her menstrual periods had become irregular, with lengthening intervals between periods. Approximately one year before admission she had begun to have intermittent episodes of fever associated with general malaise, backache, pain in the right flank, and a sensation of fullness in the upper abdomen. Studies at that time had failed to explain her symptoms on the basis of an infective agent. These studies included complete blood counts, urinalyses, routine serum agglutination for typhoid groups and for Brucella, heterophile antibody titer, gross liver function studies, and repeated chest roentgenograms which showed some elevation of the right leaf of the diaphragm and possible displacement of the heart to the left. Shortly following these studies the febrile attacks had subsided, as had the other symptoms, with the exception that the patient did not again feel entirely well. A sense of discomfort in the throat had led to a tonsillectomy in August 1951. However, thereafter she continued to lack energy and from time to time was again aware of a sense of fullness in the epigastrium. Her periods ceased entirely in the winter of 1952, and pregnancy was suspected but was ruled out. Three weeks before admission to the hospital on May 19, 1952, she again developed fever, associated with considerable pain in the epigastrium and right flank. At that time an intravenous pyelogram, barium enema, upper gastrointestinal examination, and cholecystogram were done. All showed an extrinsic mass situated in the right upper quadrant of the abdomen with displacement of the surrounding organs (Figure 29).

*This case report was published in the American Surgeon and is here reproduced in detail (103).

At this point the patient was referred to the author and the following additional findings were elicited: Her voice sounded slightly "throaty" to the examiner and in response to questioning the patient stated that, while she had noted no particular change in her speaking voice, she could no longer sing high notes The suprapubic hair distribution was definitely of the male type, and she stated *that this distribution had developed only during* the past six months. During this time she had noted also an increase in the hair about the nipples and on the upper lip, though neither of the last two findings was particularly prominent. Her breasts were small and flat

An abdominal mass which was palpable in the right upper quadrant moved downward on deep inspiration, descending almost to the umbilicus It was firm and was not tender to palpation or fist percussion Although the mass seemed to be adherent to the liver, an indentation was felt between the two which led the examiner to suspect that the main portion of the mass was not liver The mass was irregular and seemed to be lobulated There was no auscultatory bruit.

The pelvic examination revealed the probable identity of the mass The clitoris was prominent, being approximately 2 5 centimeters in length A clinical diagnosis of masculinizing tumor of the right adrenal cortex was made.

The laboratory findings substantiated the clinical diagnosis. The twenty-four-hour urinary excretion of total neutral 17-ketosteroids was 280 milligrams (average normal value for females, 10 milligrams) and the excretion of corticoids was 30 milligrams (average normal for laboratory, 5 to 8 milligrams) Thus, while the urinary excretion of both groups of steroids was elevated, the *excretion of 17-ketosteroids was enormously and* preponderantly increased, resulting in almost purely masculinizing features (the adrenogenital syndrome) with-

out such features of Cushing's syndrome as apparent obesity, hypertension, striae, and glycosuria. The fasting blood sugar level was 85 milligrams per 100 milliliters The serum carbon dioxide combining power was

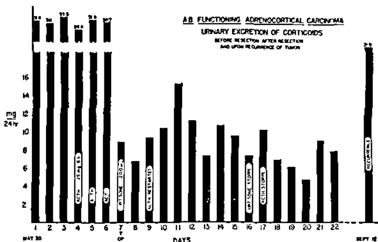


Figure 30 A B Functioning Adrenocortical Carcinoma, Urinary Excretion of Corticoids before Resection, after Resection, and upon Recurrence of Tumor. On admission the patient was excreting 31 milligrams of corticoids per 24 hours, approximately five times the normal level The administration of ACTH preoperatively did not increase the elaboration of corticoids by the tumor, which was specializing in the formation of androgens rather than 11-oxysteroids The excretion of corticoids fell precipitously to normal levels during the twenty-four-hour period in which the operation was performed It was considered that this was indicative of partial atrophy of the opposite adrenal When ACTH was stopped on the seventeenth day there was a progressive decline in the excretion of corticoids for three days, followed by higher levels Again, this was considered to reflect a partial suppression of the pituitary-adrenal axis by the administration of cortisone and/or ACTH On September twelfth the patient returned for a follow-up visit and the level of excretion of corticoids was found to be 22 milligrams per 24 hours, approximately four times the normal level Shortly thereafter *metastases were palpable in the liver* (Hardy, J D Urinary steroids in adrenocortical tumor *Ann Surg*, *138* 766, 1953)

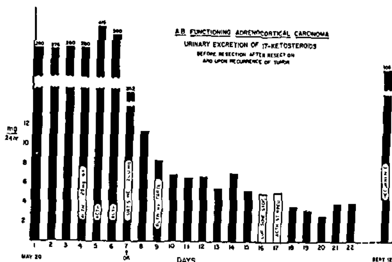


Figure 31 A B Functioning Adrenocortical Carcinoma, Urinary Excretion of 17-ketosteroids before Resection, after Resection, and upon Recurrence of Tumor Before operation this twenty-eight-year-old female with the adrenogenital syndrome was excreting 280 milligrams of 17-ketosteroids per 24 hours, approximately twenty-eight times the normal amount Despite this high level of excretion, however, the administration of 25 milligrams of ACTH intramuscularly every six hours resulted in a further increase in the urinary excretion of 17-ketosteroids to 415 milligrams Following removal of the tumor there was a precipitous fall in the excretion of these steroid products to a level of 33 milligrams during the twenty-four-hour period in which the operation was performed, the surgery being completed after only approximately two of the twenty-four hours had elapsed. This rapid fall reflected partial atrophy of the adrenal opposite the functioning adrenocortical carcinoma. When the ACTH administered postoperatively (given to stimulate the atrophic adrenal to further activity) was stopped on the seventeenth day of the study, there was a decline in the excretion of both corticoids and 17-ketosteroids for the next three days, followed by a more normal level This was considered indicative of the fact that the administration of cortisone and or ACTH had resulted in a partial temporary suppression of the activity of the pituitary-adrenal axis When the patient returned for follow up on September twelfth it was found that the 17-ketosteroid excretion had increased to 105 milligrams per 24 hours (Hardy, J D Urinary steroids in adrenocortical tumor *Ann Sur*, *138* 766, 1953)

19 milliequivalents per liter and the serum chloride level was normal Preoperative serum sodium and potassium analyses were lost through a technical mishap. The fasting total eosinophil count was 58 cells per cubic millimeter, a value considered to be somewhat low. The non-protein nitrogen level of blood was normal. She was prepared for operation with injections of ACTH (Figures 30 and 31).

Operation

Under endotracheal anesthesia the abdomen was explored through a right subcostal incision, and an encapsulated right adrenal tumor the size of a volleyball was exposed (Figure 32) The surface of the tumor was traversed by many large veins, and it was found to be firmly adherent to the under surface of the right lobe of the liver, the right leaf of the diaphragm, the inferior vena cava, and the upper pole of the right kidney The incision was extended both medially and laterally, and attention was first directed to separating the tumor from the right kidney. This proved to be relatively simple once the extremely vascular connections had been divided and the proper cleavage plane identified, which involved removing the renal capsule. It was believed that the inferior adrenal artery, a branch of the renal artery, had been divided and ligated with the many other connecting vessels, but this was not the case As the large tumor was delivered into the wound this vessel was avulsed from the renal artery, and the defect in the renal artery was closed with No 00000 Deknatel silk The tumor was thereafter successively freed from the diaphragm, liver, and the vena cava The vena cava was densely adherent to the tumor over a distance of almost 8 centimeters, and not until it had been separated from the tumor by alternate blunt and sharp dissection was it possible to visualize, ligate, and divide the large

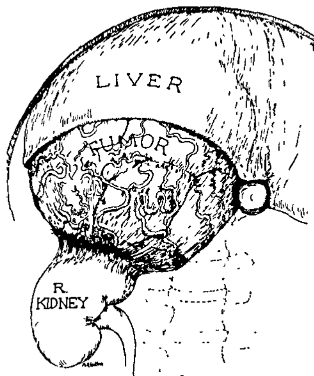


Figure 32 Right Adrenocortical Tumor This large tumor had displaced the gallbladder into the left upper quadrant (Hardy, J D, Alley, F H, Jones, R S., and Bowerman, E P *Am Surgeon*, *19* 837, 1953)

adrenal vein and the superior and middle adrenal arteries A perforation in the tumor capsule the diameter of a finger tip was produced at the point where the adrenal vein emerged from the mass to enter the inferior vena cava Otherwise the encapsulated carcinoma was removed intact

The size of the tumor, together with the extensive and extremely vascular adhesions, resulted in much venous oozing along the under surface of the liver and the right leaf of the diaphragm, and this eventually had to be

controlled with moist gauze packs until the tumor could be delivered and better exposure of the bleeding surfaces secured * There were brief intervals of hypotension during the operation, but these responded readily to the rapid infusion of blood. Even after all actively bleeding points had been ligated it was found impossible to control with sutures the continuous ooze from the large denuded under surface of the right lobe of the liver. Accordingly, the liver bed was packed with gauze rolls, the ends of which were brought out through a stab wound The wound was then closed with No 30 stainless steel wire.

Postoperative Management

At the close of the operation, which lasted two hours, the condition of the patient was judged to be satisfactory. She had received 50 milligrams of cortisone intramuscularly at the time the adrenal vein was divided, and she was placed on a postoperative dosage of 50 milligrams intramuscularly every six hours. A slow but continuous intravenous drip of 5 per cent glucose in 0 85 per cent saline solution was maintained. Five milligrams of desoxycorticosterone acetate were given intramuscularly, and penicillin was administered prophylactically Adrenocortical extract was not given but was held in ready reserve A close watch was maintained for a rise in temperature, an unduly rapid pulse, or a fall in blood pressure, should the appearance of any of these signify impending adrenal crisis The urinary output was closely followed, and morphine was used sparingly for pain

Seven hours postoperatively the rectal temperature

*The difficulty in securing adequate exposure of the vascular adhesions between the tumor and the diaphragm in this case led to the use of the thoracoabdominal incision through the eighth interspace in two subsequent cases, with complete satisfaction

had risen to 103° F. (Figure 33). Cold sponging was begun to control the fever, but two hours later the temperature had increased to 104.2° F., where it was to hover for almost thirty-six hours. However, since the blood pressure was satisfactory and since the urinary output was good, no adrenocortical extract was given at that time. Forty-two hours following the operation she experienced a definite if ill-defined crisis which was manifested by fever, apprehension, restlessness, dyspnea (40 per minute), tachycardia (130 per minute), nausea, and mild disorientation. Great difficulty was experienced in maintaining the rectal temperature below 104° F. despite continuous sponging with a cold alcohol-water mixture. The lungs were clear to auscultation and the blood pressure was 142/70.

The exact etiology of these symptoms was uncertain. As it was possible that the replacement therapy might have resulted in an overloading of the circulation, particularly in view of the fact that the blood pressure had not fallen but had actually risen somewhat, only 10 milliliters of cortical extract were administered intravenously. Aspiration of the stomach netted only 10 milliliters of bile-stained fluid, but the intramuscular injection of prostigmine given for moderate abdominal distention resulted in the passage of a considerable amount of flatus. Whatever therapy was most effective, the symptoms of nausea and dyspnea presently began to subside, and the next morning, almost exactly forty-eight hours after the operation, a rather sudden profuse sweating was followed promptly by a fall in rectal temperature from 104° F. to 101° F. Thereafter convalescence progressed uneventfully.

The packing was easily withdrawn in stages, and the patient was allowed to travel to her home 400 miles distant on the sixteenth postoperative day. After about two months her breasts enlarged, and the menstrual periods

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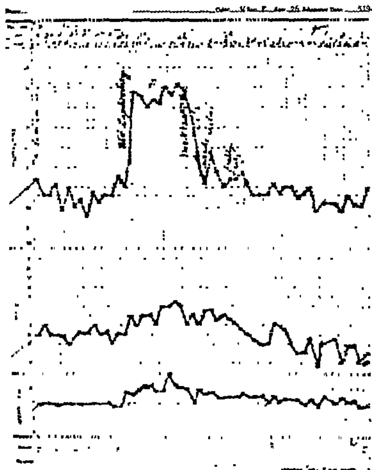


Figure 33 Clinical Chart Following Resection of Functioning Adrenocortical Tumor Four hours following the transabdominal resection of the large tumor shown in Figure 32 the patient's temperature spiked to 101° F, where it was to remain for approximately forty-eight hours despite all therapy. Febrile episodes of

E P . *Am Surgeon, 19* 640, 1953.)

resumed *Unfortunately, four months later the urinary* excretion of 17-ketosteroids was again elevated, and she died soon thereafter of hepatic metastases

Urinary Excretion of 17-ketosteroids and Corticoids (104)

Preoperative Admission Data

17-ketosteroids (Figure 31). The carcinoma was one which was secreting enormous amounts of androgenic substances, excreted in the urine as 17-ketosteroids. This *finding established the identity of the right upper* quadrant mass in the abdomen, and it explained the masculinization which had occurred in the preceding months. The level of 17-ketosteroid excretion (280 milligrams) was approximately twenty-eight times normal.

Corticoids. As is frequently the case, this tumor was secreting increased amounts not only of androgenic substances but also of corticoids (11-oxysteroids, 21-carbon atom compounds such as A, B, C, D, E, and F). In Figure 30 it may be seen that the patient was excreting 30 milligrams of these substances each twenty-four hours (4 to 5 times the normal level). Thus one might have anticipated a mixed type of clinical and physiologic picture to accord with the mixed pattern of increased steroid excretion found in the urine Actually, however, so great was the preponderance of the increased androgen production over the increased corticoid production that the physical and physiologic changes were almost entirely those produced by androgenic steroids.

ACTH and the Secretory Activity of the Tumor

In Figures 30 and 31 it may be seen that when a dose of 25 milligrams of ACTH was administered intramuscularly every six hours, beginning three days before the operation, *the urinary excretion of 17-ketosteroids* promptly increased from the previous level of 280 to 415

milligrams per 24 hours. Yet, the urinary excretion of corticoids was not affected. Therefore, the preoperative administration of ACTH would appear to have been of little value in saturating the tissues with 11-oxysteroids, the steroids most desired to diminish the likelihood of adrenal crisis following resection of a tumor.

The Desaturation of Body Tissues of Steroids Following Removal of the Tumor

In Figures 30 and 31 it may be observed that the urinary excretion of both corticoids and 17-ketosteroids fell to a normal level within forty-eight hours following the operation, despite the very high level of 17-ketosteroid excretion which had been present *immediately before operation*. The patient received 50 milligrams of cortisone intramuscularly every six hours for the first day or so postoperatively, but we and others* have observed that in normal subjects this dosage may not always materially affect the excretion of corticoids. The fact that forty-eight hours were required for the steroid excretion to drop to normal levels following removal of the tumor is in accord with the clinical impression *that if the patient has not required supportive therapy to prevent crisis by the end of forty-eight hours, he usually will not require elaborate supportive therapy thereafter.*

Does the Injection of Exogenous ACTH Result in a Diminished Production of Endogenous ACTH, as Reflected in a Decreased Adrenocortical Function?

It has often been stated that the administration of ACTH and/or cortisone in effective doses results in a suppression of the usual activity of the patient's pituitary-adrenal system, and that in patients so treated there may

*Krupp, M. A., Engleman, E. P., Welsh, J. E., and Wrenn, H. T. Measurement of the excretion of cortisone and compound F, using the Porter-Silber method. *J. Clin. Endocrinol. & Metab.*, 12: 1163, 1952.

occur a period of temporary relative adrenocortical insufficiency following the withdrawal of exogenous ACTH. Certain evidence presented in Figures 32 and 33 would appear to support this hypothesis. Following the withdrawal of ACTH on the tenth postoperative day (the seventeenth day of observation) the level of excretion of both corticoids and 17-ketosteroids fell progressively for three days, following which both levels returned simultaneously to relatively normal values. Though these changes were not great if expressed in absolute values, they were substantial if expressed on a percentage basis While the possibility of random variations has to be considered, the timing and the uniformity of the downward trend would appear to be of significance. The data seem to indicate that pituitary-adrenal activity may have been diminished by the administration of ACTH and/or cortisone.

Steroid Excretion Upon Recurrence of the Adrenal Carcinoma

Five months after operation the patient had begun to lose her appetite and to feel weak, but at first no metastases were definitely palpable However, the urinary steroid excretion studies noted in Figures 32 and 33 revealed that the excretion of corticoids had again risen to 22 milligrams per 24 hours and the excretion of 17-ketosteroids to 105 milligrams per 24 hours Soon hepatic metastases became evident on physical examination and several weeks later she died

Chapter VIII

HYPERADRENOCORTICISM

Classification of Types and Differential Diagnosis

Classification

AN UNDERSTANDING of the several types of clinical pictures which may be encountered in patients having adrenocortical tumors or hyperplasia is facilitated if one considers the various clinical syndromes on the basis of the specific hormonal imbalances which may produce them. It has previously been mentioned that the adrenal cortex is comprised of three or more less well-defined zones These are, again, the zona glomerulosa or outer zone, which apparently secretes steroids that influence fluid metabolism, the zona fasciculata or middle zone, that may secrete the 11-oxysteroids which chiefly influence protein and carbohydrate metabolism; and the zona reticularis or inner zone, which may secrete androgens

In addition, there are adrenocortical estrogens. The physiologic importance of these substances in normal subjects has yet to be clarified, but certain adrenocortical tumors secrete large amounts of these estrogenic substances which can produce feminization in men Finally, other adrenocortical hormones are likely to be identified.

In Figure 34 is presented an outline which shows the relationships which exist between the several adrenocortical hormones and the clinical pictures which are commonly observed in patients with hyperadrenocorti-

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sexual hair, and hypertension In addition to these striking physical findings one may encounter profound alterations in the metabolic processes of electrolytes and water, and of glucose, fat, and protein Definite polycythemia and hypochloremic, hypokalemic alkalosis may be present, and an elevated blood sugar and diabetic type of glucose tolerance curve are frequently observed.

A predominant increase in the excretion of androgens in women or in children results in the *adrenogenital syndrome*. Among the stigmata of masculinization which appear in women are increased muscular development with a change in body contour, a bass voice, increased hair growth which conforms to the male sexual pattern, enlargement of the clitoris, and a loss of libido. Marked metabolic alterations and arterial hypertension are usually not observed in this syndrome.

More common than either the clear-cut Cushing's syndrome at one extreme, or the adrenogenital syndrome at the other extreme, are *mixed clinical pictures* which result from an increased secretion by an adrenal tumor or hyperplasia of both 11-oxysteroids and androgens It is in the cases of mixed clinical pictures, particularly when only one or two of the features of either or both syndromes are present, that a study of the urinary excretion of steroids is particularly helpful in permitting a definite diagnosis of the pathologic physiology of the adrenocortical secretory mechanism Even so, it is at times impossible to demonstrate endocrine dysfunction by the methods now available

Finally, one may occasionally encounter *feminization*, due almost always to the presence of a tumor which is secreting increased amounts of estrogens In males the tumor is in the adrenal cortex but in females it may be situated in the ovary Striking gynecomastia may be

cism. Broadly speaking, an increase in the elaboration of 11-oxysteroids (compounds E, F, and others) (105, 106) results in the clinical syndrome which is recognized as *Cushing's syndrome* (107). The more prominent physical manifestations of this condition are the buffalo type of obesity, wasting of the muscles, moon face, purple striae, generalized hirsutism which does not particularly involve

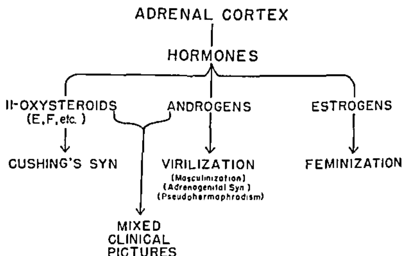


Figure 31 Hormones of the Adrenal Cortex The secretion of 11-oxysteroids is approximately the same in men and women, and the physical and metabolic changes produced by over-production of these cortisone-like hormones are similar in the two sexes An over-production of androgens results in masculinization of the female but produces little change in the adult male Precocious development of the secondary sex characters will be noted in male children and infants Over-production of estrogens may cause feminization in males but would hardly be noticed in an adult female, though precocious development of the secondary sex characters would be observed in female children Therefore, the clinical picture which is produced by the over-production of adrenal hormones will depend upon the type of hormones that are being over-produced, the sex of the patient, and the age of the patient

suggests that the effects of androgen become manifest after the eleventh or twelfth week of fetal life when the differentiation of the genital duct is complete, and before the fifth month when the normal urethral and vaginal relationships are attained At birth the clitoris is found to be hypertrophied, resembling a hypospadial penis and is bound ventrally by fibrous cords extending backward from the under surface. By examination with the urethroscope or with roentgenograms after the injection of lipidol it is usually possible to demonstrate the communication of the urethra with the vagina.

Differential Diagnosis of Adrenocortical Hyperfunction

The diagnosis and the differential diagnosis of hyperadrenocorticism may be easy or it may be difficult, in any given case Neither the completely developed Cushing's syndrome nor the completely developed adrenogenital syndrome is easily overlooked At the very least, the observer will make a diagnosis of endocrine abnormality and will suspect adrenocortical dysfunction. However, as with most clinical conditions, the completely typical picture of either of these syndromes is rarely encountered. One may be consulted by the patient who has neither the clear-cut picture of Cushing's syndrome nor the clear-cut picture of the adrenogenital syndrome, but who presents certain manifestations which may be identified with either or both syndromes

A particularly difficult diagnostic problem is that of deciding whether or not the female patient with a moderately increased amount of body hair actually has abnormal adrenocortical or other endocrine activity (111). The basic hair pattern of the individual is genetically determined and persons of different racial extraction vary widely in this respect. Over and above the genetic in-

observed in adult males who have this type of adreno-cortical tumor (108).

Advancing a step further—and bearing in mind that each of the three broad types of adrenal hormones has its specific chemical potentialities—the clinical picture which will be produced in a given person will depend not only upon which of the hormones (11-oxysteroids, androgens, or estrogens) are being over-produced but also upon the age of the patient and the sex of the patient. The variations in adults have been described. Children with Cushing's syndrome may be bizarre little individuals indeed, being somewhat stunted in growth and exhibiting poor musculature and obesity. The secondary sex characters are not primarily altered.

In children with the adrenogenital syndrome physical manifestations vary according to the sex of the patient and the age of onset (109, 110). If adrenal hyperplasia occurs in the male child prior to birth, macrogenitosomia precox may be present (precocious development of body and genitalia) If the hyperplasia appears after birth, sexual precocity and accelerated general body development may be observed during childhood

If the over-production of androgens by the adrenal cortices occurs in the female in utero, the condition gives rise to a rather uniform type of female pseudohermaphrodism (Wilkins) (109, 110). The patients have ovaries, and the Mullerian duct system undergoes normal female development to form fallopian tubes, uterus and vagina, while the Wolffian ducts disappear However, the genital duct continues to open into the urethra, forming a persistent urogenital sinus as in the male, whereas in normal females the urogenital sinus develops into a separate urethra and vagina which open into the vulva. Wilkins further states that this abnormality of sex differentiation

suggests that the effects of androgen become manifest after the eleventh or twelfth week of fetal life when the differentiation of the genital duct is complete, and before the fifth month when the normal urethral and vaginal relationships are attained. At birth the clitoris is found to be hypertrophied, resembling a hypospadial penis and is bound ventrally by fibrous cords extending backward from the under surface. By examination with the urethroscope or with roentgenograms after the injection of lipidol it is usually possible to demonstrate the communication of the urethra with the vagina.

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A particularly difficult diagnostic problem is that of deciding whether or not the female patient with a moderately increased amount of body hair actually has abnormal adrenocortical or other endocrine activity (111) The basic hair pattern of the individual is genetically determined and persons of different racial extraction vary widely in this respect Over and above the genetic in-

fluences, however, the amount and distribution of body hair is influenced also by the 11-oxysteroids, androgens, and estrogens. Wilkins (109, 110) has made the point that sexual hair (facial, pubic, and axillary), which is influenced particularly by androgens and estrogens, should be considered apart from other body hair. Body hair other than sexual hair may be increased by the administration of large amounts of cortisone. We have seen that the presence of a high level of circulating androgenic substances may eventually result in partial baldness, and it has been reported that in some cases of alopecia areata the bald area may become covered with hair during cortisone therapy. It will be recalled that in some respects cortisone and androgens are physiologic antagonists.

Urinary Steroid Excretion in States of Hyperadrenocorticism

While it is true that the abnormal endocrine function is first suspected on the basis of the history and the physical examination, the specific chemical abnormality can best be identified through the measurement of hormonal breakdown products excreted in the urine. The biochemists have made tremendous strides in recent years in unraveling the hormonal bases for the various clinical pictures of endocrine dysfunction. Although a great many separate compounds have already been identified in the secretions of the adrenal cortex, for routine surgical purposes it has been enough to measure the urinary excretion of corticoids, 17-ketosteroids and, occasionally, of estrogens.

The measurement of corticoids in the urine may indicate whether or not the production of 11-oxysteroids is increased Since these substances come from the adrenal cortices alone, an increased level of excretion indicates adrenocortical hyperfunction, though one cannot know whether this is due to tumor or to hyperplasia Further-

more, the diagnosis of increased adrenocortical activity does not preclude the possibility that the stimulus for this increased adrenocortical activity may not be a basophile adenoma of the anterior pituitary gland. Even so, almost all workers now agree that the signs and symptoms and physical changes produced by hypothalamic lesions or by the basophile adenoma of the pituitary are due to the stimulation of the adrenal cortex by ACTH. The therapeutic implications of this fact are analogous to those which exist in the surgical management of hyperthyroidism Excisional therapy is directed at reducing the amount of functional adrenocortical tissue

If the excretion of corticoids is increased and the level of 17-ketosteroid excretion not increased or only slightly so, the hormonal imbalance which produces Cushing's syndrome is present (112). If the urinary excretion of 17-ketosteroids (derived chiefly from androgens) is significantly elevated in the presence of no elevation or only slight elevation in the excretion of corticoids, the hormonal imbalance which generally leads to the development of the adrenogenital syndrome is present. However, in contradistinction to the near certainty in Cushing's syndrome that to be effective the therapeutic attack must be made upon the adrenal glands (in the absence of a rare misplaced adrenal rest in the ovary), an elevation of the level of 17-ketosteroid excretion may indicate adrenocortical hyperplasia or adrenocortical tumor, but it may also indicate the presence of an ovarian arrhenoblastoma. Testicular tumors can usually be palpated.

The fractionation of the 17-ketosteroids, where facilities exist, may be of diagnostic aid The alpha fraction is secreted by both the testis and the adrenal cortex, but the beta fraction is secreted by only the latter Normally and in hyperplasia, the beta fraction represents only 5 to

15 per cent of the total excretion, but in the presence of an adrenal tumor the beta fraction may be greatly increased.

If the level of excretion of 17-ketosteroids is elevated and the patient's symptoms and physical changes are of many years' duration, then the diagnosis will usually be that of adrenocortical hyperplasia, rather than adrenocortical tumor or ovarian tumor. Occasionally a benign adrenocortical adenoma may be present for years without producing marked changes.

The administration of cortisone may be expected to cause a sharp fall in the level of excretion of 17-ketosteroids if the diagnosis is that of adrenocortical hyperplasia; however, in the presence of adrenocortical tumor (and probably in the presence of an arrhenoblastoma of the ovary) the administration of cortisone has not resulted in a normal level of excretion of 17-ketosteroids in the cases which have been reported in the literature (113-119). This is an important consideration for, as we shall see, operation upon patients with adrenocortical hyperplasia producing the adrenogenital syndrome may not be necessary and, in fact, may be contraindicated In patients with adrenocortical hyperplasia which is producing Cushing's syndrome, on the other hand, operation will usually be necessary, even where the diagnosis is not in doubt, for surgical therapy is the only therapy which gives even moderately satisfactory results at the present time

In infants and children it may be difficult to differentiate adrenocortical hyperplasia with pseudohermaphrodism from normal adrenal function with genetic pseudohermaphrodism. Wilkins (110) suggests that if pubic hair, increased osseous and somatic development, and an increase in 17-ketosteroid excretion appear after birth, the diagnosis is probably that of adrenocortical hyper-

plasia with pseudohermaphrodism If the enlarged clitoris together with other signs of abnormal sexual development have been present from birth, with no development of pubic hair or increase in 17-ketosteroid excretion, the condition is probably due to a genetic defect in sexual development. Furthermore, if in such an individual, as noted previously, the administration of cortisone produces a fall in the excretion of 17-ketosteroids, the condition is probably not due to tumor and certainly not due to a malignant tumor. Malignant tumors usually secrete much greater amounts of androgens than do benign tumors or hyperplastic adrenals

A lesion which is producing a *feminizing syndrome* in an adult male may be producing an absolute excess of estrogens and these can be measured in the urine by the method of Jailer (120). This method has been found to afford data that usually compare reasonably well with those gained by the more tedious biologic assays. These estrogens are being secreted by the adrenal cortex, and are usually due to the presence of an adrenocortical tumor (108, 121).

The Management of Hyperadrenocorticism

Cushing's Syndrome

In addition to Cushing's classic description (1932) of the syndrome which now bears his name (107), a perusal of the almost equally classic contribution of Fuller Albright (37), delivered under the auspices of the Harvey Society of New York in 1943, is most informative

Since as noted previously it is now agreed that most if not all the signs and biochemical alterations observed in Cushing's syndrome are due to over-activity of the adrenal cortex resulting in the elaboration of excessive

amounts of 11-oxysteroids (122), it is clear that the management of this condition must be directed toward the reduction of this hyperactivity. Even should the primary stimulus be derived from a basophile adenoma of the anterior pituitary gland, because of its minute size this lesion in the pituitary rarely if ever produces pressure symptoms As noted, just as the surgeon does not extirpate the pituitary because of the over-production of the thyroid stimulating hormone (TSH) which resulted in hyperthyroidism, but directs his therapy at reducing the secretion of thyroxine by excising a portion of the thyroid gland, so will he direct his therapy to the adrenal cortex in Cushing's syndrome

Medical Management of Cushing's Syndrome The medical therapy in this condition has not been conspicuously successful, but it has shed light upon certain of the underlying pathologic mechanisms. Since many of the abnormal findings in Cushing's syndrome were considered to be the result of a deficiency of protein, and since testosterone propionate was known to be an agent which stimulated protein synthesis, this compound was administered to individuals with this disease in 1941 by Albright (37) The results were encouraging The patients went into positive nitrogen, calcium, and phosphorus balances, and they became stronger and gained weight.

In 1949 Bartter, Forbes, Jeffreys, Carroll and Albright (123) presented more recent studies concerning the therapeutic results and probable mode of action of testosterone propionate in the therapy of Cushing's syndrome in females It was concluded that testosterone produces the beneficial effects of a marked anabolism of protoplasm and a decrease in 11-oxysteroid secretion by one or more of the following mechanisms. 1. Inhibition or neutrali-

with regard to the plasma electrolytes. These workers noted the persistent tendency toward alkalosis which was present in addition to the other characteristic features of Cushing's syndrome. They noted further that the disturbances in potassium and other electrolytes which occurred in Cushing's syndrome were almost exactly opposite to those which are observed in Addison's disease. It was noted further that the administration of potassium chloride produced normal levels of potassium, chloride, and carbon dioxide combining power, though the amount given was much less than the amount of sodium chloride which had previously been given in an effort to correct the condition.

We now know, of course, that precisely this same picture can be produced, and commonly is produced, by the therapeutic administration of cortisone or ACTH. It is important to provide adequate amounts of potassium chloride for patients receiving this therapy.

Surgical Management of Cushing's Syndrome. Despite the beneficial effects of testosterone administration, the long term results of the medical treatment of this condition have been disappointing, and during recent years subtotal or total adrenalectomy has been employed with increasing frequency in adrenocortical hyperplasia producing Cushing's syndrome (129, 130, 131, 132, 133) Moreover, there is no test which will differentiate an adrenocortical tumor from adrenocortical hyperplasia in Cushing's syndrome with the degree of certainty that accompanies the use of cortisone therapy in distinguishing between a tumor and hyperplasia in the adrenogenital syndrome In our opinion, surgical exploration is justified and indicated in patients with Cushing's syndrome — and in all other instances where the diagnosis is in doubt.

If a tumor is encountered that adrenal should be re-

lents per liter, and the serum carbon dioxide combining power 41 milliequivalents per liter. The patient's diabetes was sufficiently severe to require insulin, and hypertension and osteoporosis with collapsed vertebrae were present. The urinary excretion of corticoids was markedly elevated. The intravenous administration of 28 grams of potassium chloride (12.9 milliequivalents of potassium per kilogram per hour) restored the serum electrolyte pattern and the electrocardiogram to normal in four hours. Twenty-one grams of potassium chloride were retained in an eight-hour period. Twenty-four hours later the serum potassium level had declined to 3.72 milliequivalents per liter, and the carbon dioxide combining power was now 31.5 milliequivalents per liter. In nine days the serum electrolytes had returned to the original levels. At this point 100 milligrams of testosterone propionate were given daily for nine days, and this produced a decline in the serum carbon dioxide combining power from 38.8 to 21 6 milliequivalents per liter, the serum potassium remaining low (3 0 milliequivalents).

These findings were considered to be consistent with the view of Willson, Power, and Kepler (127) that the alkalosis and hypokalemia which are frequently observed in Cushing's syndrome are secondary to the intracellular potassium depletion. In a carefully conducted study Elrel and Pearson (39) have likewise presented evidence which further substantiates the role which hypokalemia and alkalosis play in producing a portion of the picture of Cushing's syndrome The potassium deficit, hypokalemia, and metabolic alkalosis were corrected by the administration of potassium chloride

Even as early as 1937 McQuarrie, Johnson and Ziegler (128) studied a patient with Cushing's syndrome and contrasted the findings with those in Addison's disease

with regard to the plasma electrolytes. These workers noted the persistent tendency toward alkalosis which was present in addition to the other characteristic features of Cushing's syndrome. They noted further that the disturbances in potassium and other electrolytes which occurred in Cushing's syndrome were almost exactly opposite to those which are observed in Addison's disease. It was noted further that the administration of potassium chloride produced normal levels of potassium, chloride, and carbon dioxide combining power, though the amount given was much less than the amount of sodium chloride which had previously been given in an effort to correct the condition

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If a tumor is encountered that adrenal should be re-

moved in its entirety, since cortical neoplasms are commonly malignant.

If adrenocortical hypertrophy is encountered, we believe all of one adrenal and most of the other should be resected. The segment of adrenal tissue remaining should be small, for hypertrophy (hyperplasia) is common even when only a small segment of gland is left.

The availability of cortisone greatly lessens the gravity of the situation should adrenocortical insufficiency follow resection and, since the hormonal imbalance of Cushing's syndrome is incompatible with normal longevity, it is of course mandatory that the excessive production of 11-oxysteroids be adequately reduced. However, the writer is reluctant to agree with those who advocate bilateral total adrenalectomy in all patients with adrenocortical hypertrophy It is by no means impossible, or even unlikely, that some satisfactory medical treatment will be discovered in the not too distant future which will make it unnecessary to produce complete absence of adrenocortical tissue as a treatment for adrenocortical hyperplasia. Conservatism would appear justified

The mortality which follows the resection of adrenal tissue has been greatly reduced since the availability of satisfactory replacement therapy The important point is that such replacement *is* readily available, and each patient should be treated as if adrenocortical failure were expected to occur We give ACTH and cortisone preoperatively We then give 50 milligrams of cortisone during the operation, and 50 to 100 milligrams intramuscularly every six hours for forty-eight hours, or until the patient is obviously out of the danger of acute adrenal insufficiency. Larger doses of cortisone and, in the occasional patient, adrenocortical extract also may be required.

After the patient is discharged from the hospital he

must be followed by a competent physician. The development of even a minor upper respiratory infection may precipitate adrenocortical insufficiency

The Adrenogenital Syndrome

Medical Management The treatment of this condition, when it is caused by adrenocortical hyperplasia, has been much revised in the past few years by the studies of Wilkins and his associates (102, 134, 135). They have demonstrated that the administration of cortisone sharply reduces the urinary excretion of androgens and permits normal feminine development of girls who have this endocrine disorder. We and others have had similar results (136, 137, 138).

Wilkins' therapy was formulated upon the basis of sound physiologic reasoning Cortisone was administered to a patient with congenital adrenal hyperplasia in the hope that a hormone of this type, if given in quantities adequate for or greater than the normal needs of the body, might suppress the elaboration of ACTH and thus diminish the effective activity of the adrenals, including the hypersecretion of androgen The first patient that Wilkins and his associates treated was a female pseudohermaphrodite fifteen years of age who had been under observation for eleven years. In 1941, at the age of six and one-half years, the left adrenal and a portion of the right had been removed by Dr Hugh H Young without influencing the progressive virilization and hirsutism The urinary excretion of 17-ketosteroids during the years of observation averaged 42 milligrams per day Administration of cortisone in a dosage of 100 milligrams daily for fifteen days caused the 17-ketosteroid level to fall to within normal limits The urinary estrogens, determined by the fluorometric method of Jailer (120), followed the

same pattern as did the 17-ketosteroids in this subject.

Long term cortisone therapy by Wilkins and his associates (135) has resulted in the development of normal feminine characteristics in many of the female patients they have treated who are of age. They advance the thesis that before treatment is begun the secretion of both androgen and estrogen exceeds the normal level. However, the physiologic effect of estrogen on the sex organs is prevented by the excessive output of androgen. The excessive amounts of adrenal estrogen and androgen inhibit the secretion of pituitary gonadotrophins (FSH) so that the ovaries are not stimulated to secrete ovarian estrogen. Cortisone therapy inhibits the production of endogenous ACTH. The decrease of excessive androgen and estrogen production by the adrenals, resulting from the suppression of ACTH secretion, releases the normal pituitary-ovarian mechanism for the production of ovarian estrogen, and normal feminization occurs.

In the event that normal feminine development does occur, the hypertrophied clitoris can be amputated at the time of puberty and a relatively normal vaginal canal provided, since the vaginal canal is present in most of these patients The clitoris may spontaneously diminish in size.

On the basis of their relatively large experience with cortisone therapy in this condition, Wilkins and his associates have suggested the following schedule of therapy If the patient is more than eight years of age, 50 milligrams of cortisone per day is given and the intramuscular route is used initially to ensure absorption In infants 25 milligrams per day is considered adequate The maximum decrease of 17-ketosteroids should occur within five to ten days, after which one must decide by trial what the maintenance dose is to be In general, if the

patient is greater than eight years of age the maintenance dose usually is approximately 25 milligrams per day, 50 milligrams every second day, or 75 milligrams every third day, is just as effective as 25 milligrams each day. Even 12.5 milligrams daily may suppress ACTH (and androgen) production. Approximately one and one-half to twice as much cortisone is required if the hormone is given orally than if it is given intramuscularly, though the oral route is more convenient after the patient has left the hospital.

The hypertrophy or hyperplasia of the cells secreting androgens (zona reticularis?) may so encroach upon the middle and outer zones secreting the 11-oxysteroids as to produce adrenocortical insufficiency, manifested by salt loss and hypoglycemic attacks (139, 140, 141, 142, 143).

Surgical Management of the Adrenogenital Syndrome If a tumor can be demonstrated by the usual diagnostic studies, its removal is indicated However, if no tumor can be demonstrated we believe that a trial of cortisone therapy is justified when the history and the physical examination indicate that the masculinizing changes are probably due to adrenocortical hyperplasia In childhood and in adolescence the history will frequently be helpful in eliminating the probability of tumor. Moreover, the level of 17-ketosteroid excretion in a patient with the adrenogenital syndrome due to hyperplasia will generally not be much above 50 milligrams per 24 hours, whereas in the presence of a malignant tumor the 17-ketosteroid excretion may be well above 100 and, as in the patient reported in Chapter VII, may be more than 200 milligrams per 24 hours.

The development of the adrenogenital syndrome in an adult female should be considered due to a tumor until proved otherwise

To summarize, if the urinary excretion of 17-ketoste-

roids does not decline to normal levels following an adequate course of cortisone, the patient should be explored with a presumptive diagnosis of a masculinizing tumor. If a tumor is found, it should be removed. A tumor should be strongly suspected in adults.

At operation the ovaries, tubes, and uterus should always be examined if the incision permits. Although the difficulties with exposure may be considerable in obese patients, the transverse upper abdominal incision does permit examination of the pelvic organs as well as both adrenals. The thoracoabdominal incision is excellent.

Feminizing Syndromes

Feminizing tumors are rare. While certain ovarian tumors may produce precocious feminization in young girls, comparatively few feminizing adrenocortical tumors in males have been reported. The literature prior to 1948 has been reviewed by Wilkins (144), and Dohan and his associates (108) have recently reported four additional cases in which an adrenal tumor was accompanied by an increased urinary excretion of estrogens. In all four of their cases a definite tumor mass was palpable in the upper abdomen In two of the three male patients definite gynecomastia was present, and this with other findings had led to the discovery of the abdominal mass. One of their patients was a middle-aged woman who had an increased excretion of both estrogens and 17-ketosteroids due to the presence of an adrenocortical carcinoma. The fourth patient was a male whose habitus was suggestive of Cushing's syndrome Though the breasts were fat, definite breast tissue was not palpable The excretion of estrogens and 17-ketosteroids was elevated, but the excretion of corticoids was within normal limits

Chapter IX

ADRENALECTOMY FOR ESSENTIAL HYPERTENSION AND FOR MALIGNANT NEOPLASMS: SURVEY OF CURRENT STATUS

Adrenalectomy for Essential Hypertension

In recent years there has been much interest in the possible use of subtotal or total adrenalectomy as a treatment for benign or essential hypertension. Although it had long been appreciated that patients with Cushing's syndrome frequently had arterial hypertension and that patients with Addison's disease frequently had hypotension, in addition to the fact that the administration of desoxycorticosterone acetate was not infrequently associated with the development of some degree of hypertension, it was not until adequate replacement therapy became available in the form of cortisone that it was considered feasible to explore the possibility of adrenalectomy as a treatment for hypertensive disease. It was not thought that the adrenal cortex was the primary source of the stimulus *for hypertension, but it was felt that the elimina*tion in so far as possible of the salt-retaining hypertensive factors of the adrenal would ameliorate the hypertension. Such a view was in accord with the clinical experience that a low salt diet is frequently associated with a decline in the blood pressure of hypertensive individuals.

The feasibility of adrenalectomy as an effective treatment for arterial hypertension has now been studied care-

fully by Thorn and Harrison at the Peter Bent Brigham Hospital and by Wolferth, Zintel, and their associates at the Hospital of the University of Pennsylvania. In both institutions these investigative groups consisted of both surgeons and internists, and the patients were studied with great care both clinically and by various laboratory methods. In general, the patients selected for adrenalectomy, subtotal or total, were those whose disease had proved refractory to medical management. Furthermore, these individuals usually had existing damage to the heart, kidneys, or brain.

The experience to date, which has now been considerable, would appear to justify the conclusion that adrenalectomy offers at best only a moderate hope of significant and lasting improvement in any given patient Moreover, the patients elected for this type of therapy must be carefully screened, in that renal failure of a significant degree is an absolute contraindication to adrenalectomy Unfortunately, the patients who need such heroic therapy most are frequently those who already have advanced renal disease Where marked improvement has followed adrenalectomy, it has appeared to be due in large measure to the sodium chloride and water diuresis which occurred

Adrenalectomy for Malignant Neoplasms

Carcinoma of the Breast In 1951 Huggins advanced adrenalectomy as a treatment for metastatic disease of the breast, and his work to date has recently been summarized and references to the various phases of the work given (*J National Cancer Institute, 15* 1, 1954) In brief, he found that certain mammary cancers are dependent upon the adrenocortical hormones for growth. When the neoplasm is *adrenal-dependent*, bilateral total adrenal-

ectomy is often followed by regression of the metastases with re-ossification of the bone defects. Symptomatic improvement with relief of pain may be marked. Unfortunately, only a comparatively small percentage of mammary carcinomas appear to be adrenal-dependent, and it has not been possible to identify preoperatively those which will regress following adrenalectomy. Nevertheless, when the other more established endocrine measures have been exhausted in patients with advanced metastatic mammary cancer, bilateral total adrenalectomy may produce considerable improvement in perhaps a fifth of the cases. This therapy is of course not curative

Adrenalectomy for Metastatic Carcinoma of the Prostate. In advancing further the pioneer work of Huggins and Hodges upon the hormonal treatment of cancer of the prostate using castration and estrogens (*Cancer Research,* 1.293, 1941) Huggins and Scott proposed and executed bilateral adrenalectomy as a treatment for prostatic cancer (Ann. Surg, *122*.1031, 1945). This treatment was based upon the logical assumption that androgens are an activating factor in the growth of prostatic cancer and that a portion of the androgens produced in the male are produced by the adrenal cortices These studies have recently been summarized (*J National Cancer Institute, 15*.1, 1954), and similar studies by Harrison, Thorn, and Jenkins have also been published (*New England J. Med*, *248* 86, 1953)

Once again, this treatment is only palliative and is used when other methods less drastic have been exhausted. In the series reported by Harrison, Thorn, and Jenkins seven patients were subjected to total adrenalectomy for cancer of the prostate All were suffering from reactivated carcinoma with recurrent regional and metastatic disease in spite of previous orchiectomy and continuous estrogen

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Chapter X

ACTH AND CORTISONE THERAPY

The purpose of this discussion is to present a general summary of the present status of ACTH and cortisone therapy in conditions with which the surgeon may be concerned (145, 146, 147). The following topics will be considered:

I. General pharmacology
II Clinical uses and results.
III Relative and absolute contraindications.
IV. Undesirable side effects and sequelae.

General Pharmacology (148, 149, 150)

Mode of Action

The mechanisms involved in the therapeutic actions of cortisone and ACTH remain obscure, but certain general statements may be made (148) 1. The hormones do
or group of dis-
ns provoked by
by the adminis-
tration of these drugs 2. They do not destroy bacterial organisms or directly neutralize toxins and other injurious agents For example, Kass and others (63) found that the administration of ACTH or cortisone in lobar pneumonia abolished the symptoms of the patient while permitting the organisms to multiply in the blood stream 3 These hormones modify certain reactions of tissues

therapy for from six months to five years. Four had vesical obstruction with urinary retention (two complete and two partial). One had complete obstruction of the right ureter as well. Obstruction of the rectum of two patients by cancer of the prostate had required colostomy. Six had extensive osseous metastases with unremitting pain, demanding constant sedation and narcosis. In five of these the pain was completely relieved soon after total adrenalectomy. Furthermore, this improvement persisted after the cortisone dosage had been reduced to maintenance levels. Improvement of appetite concomitantly resulted in improved nutrition with a sense of well-being Regression of pelvic masses with improvement resulted in three patients and healing of osseous lesions in the spine was demonstrated in one patient five months after adrenalectomy, performed four years after orchiectomy and the institution of estrogen therapy. The sudden relief of pain after total adrenalectomy has been noted by both Huggins and Harrison to be the most dramatic result of this form of therapy.

Further studies of total adrenalectomy with subsequent cortisone therapy as a means of treatment of carcinoma of the prostate will be followed with interest It should be again emphasized that this form of treatment does not constitute a cure, but it may afford considerable palliation in some patients when other forms of therapy have been exhausted.

retical advantages over simple cortisone therapy. For example, there would be less hypofunction of the adrenal cortex when the drug was stopped. Too, cortisone does not always provide complete replacement of normal adrenocortical function. In fact, in some instances it most certainly does not. However, as mentioned, the use of cortisone has proved to be more satisfactory because of its convenience, and the response of various diseases to therapy with cortisone has been approximately as satisfactory as that with ACTH. The dosage of cortisone may be readily adjusted to counteract changes in disease activity without consideration of the adrenals' capacity to respond. Furthermore, in contrast to the variable strength of ACTH preparations, cortisone is constant in potency. Finally, certain undesirable hormonal side effects occur less frequently and are easier to control when cortisone is used, especially salt and water retention, potassium depletion, and arterio-pressor changes.

It should be noted at this point that compound F (hydrocortisone) is preferable to cortisone in certain disease conditions, particularly in the suppression of synovitis when given by local injection. Moreover, it now appears that hydrocortisone may be significantly more potent than cortisone acetate when administered orally. Hydrocortisone is available in 100 milligram ampules for intravenous use in emergencies, and in the future this compound (F) may be preferred to cortisone (E)

The maintenance dose of cortisone in most conditions may be as low as 12 5 milligrams per day by mouth. Once the acute phase of the disease has been brought under control, the patient should be maintained on the lowest dose of the hormone that will preserve clinical improvement

to noxious agents. 4. Their effect is usually temporary, and disease symptoms frequently return when the drugs are stopped.

Dosage and Administration

Cortisone may be administered intramuscularly or orally, the latter route being preferable when the patient can tolerate it. Hydrocortisone is often injected locally into the site of disease. The dose of cortisone required when the drug is given orally is not much greater than that required for intramuscular injection, and a dosage commonly employed is 50 milligrams every six hours for the first twenty-four to forty-eight hours and then 25 milligrams each six hours thereafter. The dosage of ACTH is 25 milligrams given intramuscularly each six hours, or 50 milligrams every six hours in more urgent cases. As with cortisone, ACTH should be given in generous amounts initially, until a good response has been obtained, and then the amounts reduced slowly Unlike cortisone, ACTH is not effective when given orally, since it is inactivated by the enzymes of the gastrointestinal tract Because of its convenience, oral cortisone therapy has proved to be the method of choice when it can be given by this route.

For maximal effect ACTH may be given intravenously, as this results in maximal stimulation of the adrenal cortices. Certain patients are resistant to ACTH injected intramuscularly, probably because of the effect of intramuscular enzymes in neutralizing the hormone (30) The physiological potency of 20 units of ACTH given intravenously is stated to be equivalent to approximately 200 units given intramuscularly in divided doses

The activation of the total steroid output of the adrenal cortex with ACTH would appear to provide certain theo-

mon than has previously been realized. Butterly and his associates (154) have reported Addison's disease secondary to metastases involving the adrenal glands. We have recently observed a case of Waterhouse-Friderichsen syndrome which occurred due to septicemia in a patient with a relatively minor burn wound. Cortisone therapy was strikingly effective in this instance, as it has been in similar cases recently reported in the literature (155, 156.)

Nevertheless, we have encountered relatively few patients on our active surgical service who appeared to suffer from definite adrenocortical inadequacy, even of mild degree. This of course excludes patients with obvious adrenocortical pathology or who had resection of adrenal tissue. Hume and Moore (157), and Cole, Grove, and Montgomery (158) have reported striking improvement in patients who would appear to have had some degree of adrenocortical hypofunction, though these observers could not be certain that adrenal inadequacy did actually exist.

Treatment of Adrenocortical Insufficiency. The general outlines of ACTH and cortisone therapy, of which only the latter would apply in adrenocortical hypofunction due to adrenocortical disease, have been given in the section on pharmacology. It is enough to emphasize here that it is more often too little therapy that is given than too much, and a minimum of 200 milligrams of cortisone per day should be administered if adrenocortical insufficiency is seriously suspected in a patient being subjected to surgery

Allergic Conditions

The beneficial influence of adrenocortical hormones in a wide variety of hypersensitive states has been one of the most consistent features accompanying their use

Clinical Uses of ACTH and Cortisone

Adrenocortical Insufficiency, Absolute and Relative: Diagnosis

The intiavenous use of ACTH has now provided for the first time a rather dependable test of the adrenocortical reserve (30, 151, 152, 153). In a study of forty-one normal subjects, the intravenous administration of this amount of ACTH produced an aveiage fall in the total eosinophil count of 97 per cent (30). Therefore, if the patient suspected of having relative adrenocortical insufficiency does not exhibit at least a 50 per cent fall in the total eosinophil count following the eight-hour infusion of 20 units of ACTH, he should receive ACTH or cortisone therapy prior to, during, and following an operative

but if the eosinophil count does not fall it should not be accepted as indicating adrenocortical inadequacy and the intiavenous ACTH test should be utilized. Finally, even individuals who exhibit a minimal response to intravenous ACTH may withstand operation uneventfully (Jabbour and Hardy, Surgical Forum, vol V).

In patients with Addison's disease who must be operated upon and in patients who are being subjected to total adrenalectomy for hypertension or for neoplastic disease, 50 milligrams of cortisone should be given intramuscularly befoie opeiation and 50 milligrams (or more, if required) each six hours for the first two or three days postoperatively This should be followed by a gradual reduction of the dosage until the maintenance dose is arrived at Most patients can eventually be maintained on 25 milligrams or less of oral coitisone per day.

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Asthmatic attacks are commonly relieved, but the fundamental pathology is not altered. Exfoliative dermatitis responds in a most gratifying way in the author's experience and in that of others (159). Thedos (160) has used ACTH in the management of iodine sensitivity during bronchography.

The Prevention of Adhesions in the Chest, Pericardium, and Abdomen

The reported data (161, 162, 163, 164) are in conflict as regards the efficacy of ACTH and cortisone in the management and prevention of postoperative adhesions, whether in the chest or in the abdomen. For this reason a skeptical attitude seems justified concerning the effectiveness of these hormones in preventing postoperative adhesions in human beings.

Blood Dyscrasias Agranulocytosis, Hypersplenism, Idiopathic Thrombocytopenic Purpura, and Acquired Hemolytic Anemia

Agranulocytosis In 1952 Hart, Wraith, and Mansell (165) reported the successful use of ACTH in a case of agranulocytosis due to an amidopyrine derivative Rapid improvement in the blood and clinical picture appeared by the third day of treatment and complete recovery was effected in three weeks. More recently the value of ACTH and cortisone in this condition has been summarized (166) While the use of these hormones in this serious condition has been definitely encouraging, it is pointed out that with the use of these drugs penicillin is needed more than ever, since under certain circumstances the administration of cortisone may be followed by "spontaneous" infections.

Hypersplenism ACTH and cortisone have been effective in producing remissions in this condition, though such

remissions may be only temporary. Myers, Miller and Bethel (167) reported the use of ACTH in two cases of splenic neutropenia and rheumatoid arthritis (Felty's syndrome). The neutropenia was corrected by the daily administration of 100 milligrams for six days in one patient and for 10 days in the other patient. The rise in neutrophils occurred several days following the decrease in the eosinophil count Idiopathic thrombocytopenic purpura was particularly benefited (see below). Kierman and Hunter (168) report a similar experience.

Idiopathic Thrombocytopenic Purpura. Faloon, Greene, and Lozner (169), and Evans and Liu (170) have used ACTH and/or cortisone to study the hemostatic defect in this condition. The defect appears to be due to an abnormal vascular fragility which has been consistently responsive to adrenocortical steroid mobilization or administration In this condition there is also a decreased production or an increased destruction of platelets with poor clot retraction and poor prothrombin utilization, defects which are only irregularly corrected by hormone therapy. Faloon and his associates conclude that platelet production and vascular resistance may be separately affected by the hormones

Jacobson and Sohier (171) reported that the administration of ACTH and cortisone in three patients with idiopathic thrombocytopenic purpura was followed by a prompt increase in platelets from purpuric to normal levels and even to abnormally high levels They considered such therapy especially helpful in acute hemorrhagic episodes and in preparation for splenectomy Myers and his associates (172) have also reported the favorable effect of ACTH and cortisone in modifying the course of thrombocytopenic purpura and in producing the changes characteristic of spontaneous remissions They

point out that the failure to respond to hormonal therapy does not preclude a favorable response to splenectomy. However, patients with incomplete remissions after splenectomy may be benefited by ACTH or cortisone administration.

Thus, a most valuable use of these agents may lie in the treatment of crises and in the preparation of the patient for splenectomy. Although several remissions may be obtained with hormonal therapy, the patient eventually is likely to become refractory to the use of these agents and then it may be difficult to perform a splenectomy which usually does produce a satisfactory remission and one which is apt to be lasting.

Acquired Hemolytic Anemia. Dameshek, Rosenthal, and Schwartz (173) have examined the response of this condition to ACTH, and have observed well-defined remissions Krary and Beck (174) also reported a satisfactory remission following the use of ACTH and cortisone, but eventually the patient relapsed, as cortisone therapy was less effective, and she finally died Similar results have been reported by others Aitchison (175) reported a patient who exhibited an initial dramatic improvement that was truly life saving, but subsequent courses of ACTH and cortisone had progressively less effect Splenectomy, not done during the first remission from cortisone, had to be performed in desperation, and wound disruption very nearly resulted in death If splenectomy is to be performed, it would seem wise to utilize hormonal therapy to effect a remission and then to do the splenectomy promptly (176, 177)

Burns

The early enthusiasm in some quarters concerning the efficacy of ACTH and cortisone in the therapy of burned

patients has now largely waned. Rakor, Wight, Michel and Cope (178) carefully evaluated clinically and experimentally the influence of ACTH on the need for fluid therapy of the burn patient. Their conclusion was that ACTH does not repair or prevent the abnormal capillary permeability in burns and they found no reason to alter present therapy by the addition of ACTH. This statement is in harmony with the views of Evans and Butterfield (98) and the present writer concurs. Actually, in our laboratory we have found that the adrenocortical response to stress in the burn patient is tremendous, and there is no evidence now available which proves that in the absence of cortical failure these patients will be materially benefited by higher concentrations of these hormones.

"Collagen Diseases"

Rheumatoid Arthritis The general effects of ACTH and cortisone therapy in rheumatoid arthritis are so well known as to require little comment These agents produce a remarkable and prompt remission from the symptoms and signs of joint inflammation in a large percentage of the acute cases. Unfortunately, in most cases there is an early recurrence of the signs and symptoms when therapy is stopped, and in many cases the disease eventually becomes refractory to therapy with these agents Nevertheless, the availability of these drugs has helped considerably in the development of a more hopeful outlook in the management of these patients.

Hollander and his associates (179) have reported that compound F is much more effective than compound E (cortisone) in suppressing the synovial inflammation in rheumatoid arthritis when injected locally into the joint space (180)

Bursitis Orbach (181), and Steinberg and Roodenburg

will require such therapy. In the opinion of Hume and Moore, the indications for hormonal therapy are best defined by the process of elimination. Good surgical treatment, both supportive and technical, should precede and accompany the use of ACTH and cortisone. If after other therapy the patient still has a poor outlook for surgery or convalescence, one may be justified in giving cortisone or ACTH. In our experience, they are rarely required

The Gastrointestinal Tract, Liver, and Pancreas

Peptic Ulcer. ACTH or cortisone therapy is contraindicated in the presence of this condition (190, 191, 192, 193, 194, 195). Perforation and hemorrhage may occur

Ulcerative Colitis and Regional Enteritis Patients with ulcerative colitis are frequently dramatically improved by the administration of ACTH or cortisone. Kirsner and Palmer (196) have summarized their experience as follows ACTH does not cure but frequently results in striking remissions Though a similar clinical improvement may occur spontaneously, it is much less rapid than following hormonal therapy Relapses are frequent following hormonal therapy, but thus far in their experience the relapses seem less severe than is ordinarily the case. The mechanism of action is unknown. These results are similar to those reported by others (197, 198, 199, 200, 201).

Certain complications have occurred during this therapy in ulcerative colitis. Hemorrhage and perforation of the colon have been reported and, if the patient has been treated with ACTH as preparation for operation, the colon may rupture easily on manipulation (202).

Hormonal therapy has been less effective in the management of regional enteritis than in ulcerative colitis (203)

Hepatitis. Webster (204), and Riskin and his associates (205) have reported the use of ACTH and cortisone in the management of hepatitis. Defervescence and symptomatic relief was prompt. Though clinical relapse occurred in some, the restitution of therapy produced a rapid remission.

While noting the hopeful nature of these early reports, an editorial comment in the British Medical Journal (206) has struck a more conservative note. The lack of controlled studies is cited but it is concluded that the results, while not remarkable, do perhaps suggest that these agents should be tried in patients who are going rapidly downhill It is noted further that these agents do diminish the pruritis in jaundice and that this in itself is a worthy achievement.

Hemorrhagic Pancreatitis. In a reported instance this condition was dramatically improved following treatment with cortisone (207) The patient appeared to be dying when hormonal therapy was started, but there was sufficient improvement to permit an operation on the third day (performed on the basis of an erroneous diagnosis of ruptured gallbladder with bile peritonitis) Additional experience will be awaited with interest

Functioning Metastatic Carcinoma of the Isles of Langerhans Following the resection of a functioning malignant islet cell tumor of the pancreas, metastases in the liver again began to produce excessive amounts of insulin

promoting gluconeogenesis and by inhibiting the peripheral action of insulin Mason (41) concluded that the dose of cortisone which was required to prevent severe hypoglycemia (112 milligrams per 24 hours at the time the article was written) made it very probable that corti-

sone acted as an insulin antagonist. The patient had taken cortisone continuously for twenty-five weeks and his general condition remained satisfactory, within the limitations imposed by the diagnosis of malignancy.

Homografting

Early optimistic reports concerning the value of ACTH and cortisone in prolonging the life of homografts have now been largely discredited (208-215). It is generally agreed that these agents do not prolong the survival of split thickness skin homografts in man or in animals. This is also true of homotransplants of adrenal tissue in dogs, and one may safely anticipate that it will probably be true of homografts of all types.

Infections

The use of ACTH and cortisone in the therapy of surgical infections is a double-edged sword (216-220) In certain patients who have overwhelming infections (we are not referring here to Waterhouse-Friderichsen syndrome) the use of these drugs may act as a block between the toxic materials elaborated by the bacteria and the body cells of the host. In this way the patient may be provided with a temporary relief from the effects of the infection, to allow the body defenses to be organized and mobilized. Thus, with this aid he may survive where otherwise he might be overwhelmed by the infection This is one side of the sword. The other side of the sword is that under certain circumstances the administration of ACTH and cortisone actually increases the invasive power of bacterial organisms, and it has been demonstrated that bacteria can be passed from animal to animal in a species which is ordinarily resistant to these organisms, if the animals are concurrently treated with

cortisone. Furthermore, cortisone and ACTH alter the ability of the host tissues to react to injurious agents and a large scale necrosis may be produced without necessary tissue defensive reaction.

Martin, Schwartz, and Engel (220) *have offered the* following statement concerning the use of ACTH and cortisone therapy in the treatment of life-threatening infections (1) a specific etiological agent should be known; (2) specific antibiotic treatment should be available and chronic hormonal therapy should be avoided, and (3) adrenal overdosage may have a place in the treatment of bacterial diseases where short term diminution of the host response or retardation of toxic reactions is indicated

The infectious complications of adrenocortical hormone therapy are a constant threat to its use in all diseases. The diminution of the host response to infectious agents is so great that the danger associated with treatment is intensified by a delayed recognition of the complications

Conditions of the Peripheral Nervous System (221)

Anogenital Pruritis Fromer and Smith (222) have treated ten patients with severe anogenital pruritis with ACTH A dramatic subjective and objective improvement was observed after this therapy and this improvement had been sustained for as long as eleven months at the time of the reporting Turrell (223) obtained similar results but emphasized that ACTH therapy should not replace the conventional methods of local medication and the surgical correction of such lesions as hemorrhoids and fistula in ano. The present consensus is that the ACTH represents a valuable adjunct in the treatment of selected cases The local injection of hydrocortisone has also been effective

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Snake Bite ACTH and cortisone have been reported to produce dramatic improvement in persons bitten by poisonous reptiles.

Arachnidism. Maretic (228) has reported that a single dose of 80 milligrams of cortisone is effective in controlling the signs and symptoms due to the bites of poisonous spiders, but the author also noted that intravenous calcium gluconate is usually effective and is less expensive.

Acute Alcohol Poisoning and Delirium Tremens. The adrenal steroids have proved to be of significant value in the management of acute and chronic alcohol poisoning. Felderman and Zucker (229) state that the administration of ACTH or cortisone aids the patient in recovering more rapidly from his intoxication and makes the requirements for sedation less rigorous The number of acute psychotic states associated with chronic alcoholism was diminished Fischback, Simmonds and Pollard (230), in a discussion of the management of delirium tremens, have contrasted the therapy of the past with the modern therapy employing ACTH administered intravenously. This use of ACTH has produced marked improvement in this condition In studying experimental alcohol poisoning, Lecoq of Paris (231) has found that these hormones exert an inhibiting action upon the central nervous system effects of ethyl alcohol

Since it frequently happens that the surgeon must care for a patient who is acutely intoxicated, the value of these agents in the treatment of acute alcoholic states should be kept in mind

Thyroid Diseases

Hyperthyroidism with Crisis The relationship which may exist between thyroid activity and adrenocortical activity in thyroid crisis has previously been mentioned

The Shoulder-Hand Syndrome. The painful syndrome involving the shoulder and hand following acute myocardial infarction has been treated with cortisone by Russek and his associates (224). They reported seventeen cases all of which had previously had physical therapy, manipulation, local injections, and stellate ganglion blocks without improvement. Cortisone produced complete relief of signs and symptoms in five, marked improvement in eight, moderate improvement in three, and no significant improvement in one The striking feature of this therapy was the relief of pain in twenty-four to forty-eight hours. Joint motion was increased and the vasomotor disturbance and edema were diminished The improvement in the temperature, color, and pseudomotor activity of the hand was most gratifying. In the patients who responded readily there was no recurrence of symptoms after the drug was discontinued No thromboembolic phenomena occurred in this series These authors concluded that cortisone represents a safe and effective means of treatment in refractory cases of the shoulder-hand syndrome complicating myocardial infarction.

Herpes Zoster Several papers have appeared in the literature concerning ACTH and cortisone therapy in herpes zoster, and genuine improvement has been reported with this treatment One writer, however, reported the onset of herpes zoster during a course of cortisone therapy given for some unrelated condition, though he felt that the eruption might have been entirely incidental and not due to the hormone

Toxic Poisoning

Tetanus ACTH and cortisone therapy have had no substantial effect in the treatment of cases of tetanus (225, 226, 227).

months, the disappearance of such symptoms within two to three days following the administration of ACTH and cortisone would appear to validate the expressed optimism. Occasional relapses have been reported when the drugs were discontinued, but the restitution of therapy was again followed by a relief of symptoms and, moreover, the second course of therapy usually resulted in a permanent remission.

Periarteritis Nodosa. Beneficial results have been reported following the use of ACTH and cortisone in this condition (238), but at this time it would appear wise to reserve judgment as to what place these hormones will eventually have in its management.

Thromboangeitis Obliterans Jacques (239) has reported improvement in one case following the use of cortisone He points out that it would appear that this hormone is capable of suppressing the acute vascular inflammation and probably has potentialities for minimizing the residual obliterative endarteritis

Miscellaneous Conditions

Shock. Howard and DeBakey (240) did not find cortisone and vitamin B_{12} to be of value in diminishing the mortality in dogs subjected to hemorrhagic shock. In a somewhat different study Halpern, Denacerraf and Briot (241) found that the blood pressure was better maintained following repeated hemorrhage in adrenalectomized animals maintained on desoxycorticosterone acetate and cortisone than in the animals maintained with desoxycorticosterone acetate alone Nevertheless, the consensus is that adrenocortical hormones offer little in the management of hemorrhagic shock

Anuria. Moore and O'Donovan (242) have used cortisone in the management of acute anuria Of the four

The administration of ACTH and cortisone has produced improvement in some cases of thyroid crisis. Nevertheless, since this therapy has not been invariably effective, all other known measures of therapy should be used in treating thyroid storm. The mortality remains high.

Hypercalcemia Associated with Hyperthyroidism. Rose and Boles (232) have recently directed special attention to the hypercalcemia which is occasionally present in hyperthyroidism. Since the hypercalcemia of sarcoidosis has been treated effectively with doses of cortisone, the hypercalcemia of hyperthyroidism might well also respond to such therapy. Moreover, we have recently observed tetany in a patient receiving 400 milligrams of cortisone daily; the symptoms subsided following the intravenous administration of calcium gluconate.

The Management of Exophthalmus. Kinsell, Partridge and Foreman (233) have utilized ACTH and cortisone in the treatment and in the differential diagnosis of malignant exophthalmus On the basis of nearly two years of observation in nine patients, they concluded that systemic ACTH and local or systemic cortisone will favorably modify "thyrotropic exophthalmus." These authors believe that the beneficial results are perhaps due to the "lysis" of abnormal tissue deposited within the orbit or to the inhibition of thyrotropin production

In the limited experience of the present writer, ACTH has had little effect on the exophthalmus associated with Graves' disease.

Vascular Diseases

Temporal Arteritis The use of ACTH and cortisone in this condition has resulted in numerous favorable reports (234-237). Since when this disease is treated by other methods the symptoms commonly continue for several

Peptic Ulcer. As noted previously, ACTH and cortisone frequently have a deleterious effect upon peptic ulcer. Hemorrhage and perforation have occurred in known ulcers, and new ulcers have been produced

Diabetes Mellitus. Large doses of ACTH and cortisone have a diabetogenic effect (251), and thus they should not be used in the presence of diabetes mellitus unless the benefits to be derived are considered to be life-saving

Hypertension. As ACTH and cortisone therapy may result in the retention of salt and water, these compounds should be used with caution in the presence of hypertension

Congestive Heart Failure. The retention of salt and water which may be caused by the administration of these hormones would of course be hazardous in the presence of heart failure If these agents are imperatively needed, they should be used with full realization of the possible side effects, which might result in a further deterioration of the state of cardiac compensation.

Cushing's Syndrome The administration of ACTH and cortisone, especially if prolonged, could aggravate the metabolic alterations present in Cushing's syndrome, since an excess of 11-oxysteroids is present already

Pregnancy There is some evidence which indicates that the administration of ACTH and cortisone during pregnancy may result in harm to the fetus DeCosta and Abelman (252) found that cortisone interfered with pregnancy in the rabbit Cortisone apparently did not interfere with pregnancy in the human being, and these workers concluded that cortisone might safely be administered to pregnant women when necessary. However, the findings of Guilbeau (253) furnished suggestive evidence that the administration of these agents early in pregnancy might result in fetal anomalies Therefore, at

cases treated, three recovered. However, it was this writer's impression that the three patients who recovered might well have recovered without the benefit of cortisone therapy. Since spontaneous recovery is frequent, the use of cortisone in these cases seems inconclusive. Further studies of this nature will be required before it can be stated positively that cortisone offers significant aid in the management of this condition.

Thymic Masses. Soffer, Gabrilove and Wolf (243) have used ACTH in the management of thymic masses Five patients with an enlarged thymus were treated by the intramuscular administration of this hormone In two patients the mass was due to tumor, in one of whom the tumor was malignant. In one patient with a thymoma the reduction in the size of the mass and in the size of the metastases was striking. However, in one patient with thymic enlargement, the etiology of which was not diagnosed, there was a rapid increase in the size of the gland after four days of therapy. At present, therefore, it would appear wise to explore undiagnosed thymic masses surgically A trial of ACTH or cortisone therapy may be indicated for the temporary relief of respiratory obstruction due to thymic enlargement.

Keloids A number of reports have now appeared concerning the role of cortisone in the management of keloid formation. The use of this compound has been of little aid (244)

Relative and Absolute Contraindications to the Use of ACTH and Cortisone Therapy

Tuberculosis. The use of ACTH and cortisone in the presence of tuberculosis may result in a spread of the disease (245-250).

Peptic Ulcer. As noted previously, ACTH and cortisone frequently have a deleterious effect upon peptic ulcer. Hemorrhage and perforation have occurred in known ulcers, and new ulcers have been produced.

Diabetes Mellitus. Large doses of ACTH and cortisone have a diabetogenic effect (251), and thus they should not be used in the presence of diabetes mellitus unless the benefits to be derived are considered to be life-saving.

Hypertension. As ACTH and cortisone therapy may result in the retention of salt and water, these compounds should be used with caution in the presence of hypertension.

Congestive Heart Failure The retention of salt and water which may be caused by the administration of these hormones would of course be hazardous in the presence of heart failure If these agents are imperatively needed, they should be used with full realization of the possible side effects, which might result in a further deterioration of the state of cardiac compensation

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this time these drugs should probably be avoided in pregnancy whenever possible (254).

Psychotics and Psychopathic Personalities. It is not uncommon for a patient to develop a psychotic episode while receiving ACTH or cortisone therapy. Moreover, occasionally a psychotic patient may become lucid during therapy with ACTH and cortisone, only to relapse into the psychotic state after these drugs are discontinued. Since these agents are not curative in the presence of psychoses, conservatism is indicated regarding their use in patients with a tendency toward severe personality disorders.

Side Effects and Possible Undesirable Sequelae of ACTH and Cortisone Therapy

Cushing's Syndrome Sprague and his associates (255) have reported the appearance of Cushing's syndrome following prolonged ACTH and cortisone therapy. Among the features which developed were rounding of the facial contours, hirsutism, acne, keratosis pilaris, muscular weakness, edema, amenorrhea, cutaneous striae, mental depression, impaired carbohydrate tolerance, negative nitrogen balance, an increased excretion of corticoids, and hypochloremic, hypopotassemic alkalosis. The appearance of any of these findings should be watched for in patients receiving hormonal therapy.

Iatrogenic Adrenal Insufficiency. Many studies have indicated that following a prolonged course of ACTH and/or cortisone therapy there occurs a greater or lesser degree of functional atrophy of the pituitary-adrenal system (256-259). This is more likely to occur following cortisone than ACTH When such patients are subjected to operation they may go into relative adrenocortical failure. Thus, when a patient has been on these hormones for

a prolonged period before operation this therapy should be restarted immediately before operation and continued well into the postoperative period.

Protein Shock. Wilson (260) has reported the occurrence of anaphylactoid shock in two patients following the intravenous administration of ACTH. These reactions developed gradually and were maximal forty-five minutes after the infusion was stopped. However, such reactions must be extremely rare.

Spontaneous Infections during ACTH and Cortisone Therapy. The work of Mogabgab and Thomas (261) has previously been cited. Over-treatment with ACTH and cortisone may diminish the body's normal defenses to the point that bacteria ordinarily not invasive may become so

Hepatomegaly with Fatty Infiltration Steinberg, Webb and Rafsky (262) have reported the development of this condition following cortisone therapy. Nevertheless, such reports have not been frequent and additional evidence is needed before this can be listed as a common complication of ACTH and cortisone therapy

Retardation of Wound Healing. This possibility, attendant upon the administration of ACTH and cortisone, has been discussed earlier (263-265). Most patients manage to heal their wounds satisfactorily even when on cortisone therapy.

In an experimental study of the regeneration of skeletal muscle, Sissons and Hadfield (266) found evidence that, while the beginning of regeneration of this tissue was retarded by cortisone therapy, the ultimate course of the repair process and the integrity of the ultimate wound healing were not seriously impaired

Muller, Spencer and List (267) found no deleterious effect of cortisone on the healing of wounds of the cardiovascular system.

Shepanek (268), and Sissons and Hadfield (269) studied the influence of cortisone on the repair of experimental fractures. These workers found evidence that this hormone did inhibit the formation and maturation of callus, and that the epiphyses closed prematurely. In a single patient, Teicher and Nelson (270) have reported osteoporosis and pathological fractures following treatment with ACTH or cortisone. Patients with Cushing's syndrome often present evidence of osteoporosis and may occasionally suffer spontaneous fractures.

Thrombo-embolic Complications. Cosgriff (271) has studied 700 patients treated with cortisone or ACTH. In 28 of these patients there were 40 episodes of thrombo-embolic disease which developed during or shortly after the hormonal therapy. These vascular complications, together with the observations of hypercoagulability of the blood known to be associated with the administration of these compounds, indicate that the possibility of thrombo-embolic phenomena should be borne in mind

The Amelioriation of the Undesirable Metabolic and Clinical Effects of ACTH and Cortisone. Greeman, Weigand and Danowski (272) have used oral cation exchange resins in patients receiving cortisone or ACTH with a view to minimizing the derangement of electrolytes which commonly occurs during such therapy. However, the use of the carboxylic type of exchange resin, with equal parts of hydrogen and potassium forms, did not prevent the development of alkalosis or hypochloremia The release of potassium from the ingested resin did produce some increase in the amount of assimilated potassium, but it did not prevent the development of hypocalemia in four of five patients.

Kinsell, Partridge, Boling and Margen (273) also have attempted to modify the undesirable side effects of ACTH

and cortisone. Protein hypercatabolism results in acute ulcer penetration and perforation, diminished wound healing, decreased localization of infection, muscular weakness, osteoporosis, and diabetogenesis The retention of sodium and water results in edema, hypertension, and possibly mental derangement. The depletion of potassium results in muscular weakness and possible insulin resistance and mental derangement. To diminish these ill effects the authors suggest that the sodium intake be restricted to less than 100 to 300 milligrams per day and *that adequate potassium supplementation be given in* amounts of 20 grams or more of potassium chloride by mouth per day. In patients with a tendency to the formation of peptic ulcer, large amounts of antacids should be given. Intensive protein therapy should be administered to increase the antibodies in patients with infection, and antibiotics should also be given. To diminish the decalcification of the bones, testosterone plus calcium and vitamin D should be administered These workers emphasize that if a diet high in protein and potassium, adequate in calories, and low in carbohydrate and sodium is given, many of the undesirable effects of ACTH and cortisone therapy will be avoided (274)

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REFERENCES

1. Pontes, J. F, and Neves, D. P. Adrenal stimulation in the dumping syndrome. *Gastroenterology*, 23 431, 1953
2. Long, C N H. Factors regulating the adrenal cortical secretion, in pituitary-adrenal function A publication of the American Association for the Advancement of Science, Washington, D C, 1950, p 24
3. Gordon, M L An evaluation of afferent nervous impulses in the adrenal cortical response to trauma, *Endocrinology*, 47 347, 1950
4. Fortier, C Dual control of adrenocorticotrophin release. *Endocrinology*, 49 782, 1951.
5. Hume, D. M. The neuro-endocrine response to injury. Present status of the problem. *Ann Surg*, 138.548, 1953.
6. Recant, L, Hume, D. M, Forsham, P. H, and Thorn, G W Studies on the effect of epinephrine on the pituitary-adrenocortical system. *J Clin Endocrinol*, 10 187, 1950
7. Wolfson, W Q. Inadequacy of epinephrine as an activator of the pituitary-adrenal system *J Clin Endocrinol & Metab*, 13 125, 1953.
8. Sanberg, A. A, Nelson, D H, Palmer, J. G, Samuels, L T, and Tyler, F. H. The effects of epinephrine on the metabolism of 17-hydroxycorticosteroids in the human *J. Clin Endocrinol & Metab*, 13 629, 1953.
9. Bliss, E. I, Rubin, S., and Gilbert, T. Effect of adrenalin on adrenal cortical function. *J. Clin Endocrinol. & Metab.*, 11 46, 1951
10. Farrell, G. L., and McCann, S M: Detectable amounts of adrenocorticotrophic hormone in blood following epinephrine *Endocrinology*, 50 274, 1952
11. Cortisone versus salicylates (Editorial) *Lancet*, 2 524, 1952
12. Van Cauwenberge, H, and Betz, H. Salicylates and neuro-endocrine stimulation *Lancet*, 1 1083, 1952
13. Hailman, H F: ACTH and cortisone versus salicylates *J Clin Endocrinol & Metab*, 12 454, 1952
14. Pasqualini, R Q Salicylates, anterior pituitary, adrenals, and eosinophils *J Clin Endocrinol & Metab*, 12 1246, 1952.
15. Hetzel, B S, and Hine, D C. The effect of salicylates on the pituitary and suprarenal glands *Lancet*, 2 94, 1951
16. Bertolani, F, Lorenzini, R, and Bonati, B. Salicylates in acute osteomyelitis *Lancet*, 1 54, 1951.

31. Corcoran, A. C . Adrenal Cortex in hypertension, in pituitary adrenal function. A publication of the American Association for the Advancement of Science, Washington, D C, 1951, p 183.

32 Hardy, J D.. Adrenal cortex and postoperative gastrointestinal secretions, clinical significance of these effects *Surgery*, 29 517, 1951.

33 Long, C. N H, Katzin, B, and Fry, E G · The adrenal cortex and carbohydrate metabolism. *Endocrinology*, 26 309, 1940

34 Ingle, D J, Ward, E. O, and Kuizenga, M H · The relationship of the adrenal glands to changes in urinary non-protein nitrogen following multiple fractures in the force-fed rat *Am J. Physiol*, *140* 510, 1947.

35 Engel, F L A consideration of the roles of the adrenal cortex and stress in the regulation of protein metabolism *Recent Progress in Hormone Research*, *6* 277, 1951

36 Sprague, R G Cortisone and ACTH *Am J Med*, *10* 567, 1951.

37. Albright, F · Cushing's syndrome *Harvey Lectures*, 38.123, 1942-43

38. Whitney, J E, and Bennett, L L : Inhibition of the catabolic effect of adrenocorticotropic hormone (ACTH) in rats fed a diet high in potassium chloride. *Endocrinology*, *50* 657, 1952

39 Eliel, L P, and Pearson, O H The metabolic effects of adrenocorticotrophic hormone (ACTH) in a patient with Cushing's syndrome and acromegaly *J Clin Endocrinol & Metab*, *11* 913, 1951.

40 Long, C N H The influence of the pituitary and adrenal glands upon pancreatic diabetes, *Medicine*, *16* 215, 1937.

41 Mason, A S Functioning malignant islet-cell tumor of pancreas, primary growth removed, metastases in liver seen Recurrence of hyperinsulinism, treated with cortisone *Proc R Soc M*, *46* 305, 1953

42 Lachance, J, and Page, E . Hormonal factors influencing fat deposition in the interscapular brown adipose tissue of the white rat *Endocrinology*, *52* 57, 1953

43. Gaunt, R, Birnie, J H, Boss, W R, Enersole, W J, and Osborn, C M · The adrenal cortex in water metabolism, in pituitary-adrenal function A publication of the American Association for the Advancement of Science, Washington, D C, 1951, p 102

44 Gaudino, M, and Levitt, M F · Adrenal cortex, body water, and renal function *J Clin Investigation*, *28* 1487, 1949

45. Gaunt, R, and Birnie, J H Hormones and body water Charles C Thomas, Springfield, Illinois, 1951

46 Davis, A K, Bass, A C, Overman, R R, Hudson, V C, and Stevenson, E A Comparative effects of cortisone and DCA on ionic balance and fluid volumes of normal and adrenalectomized dogs *Am J Physiol*, *166* 493, 1951

17. Morel, E., Bonvallet, M., and Stutinsky, F.: Responses eosinopeniques emotionnelles et developpement du cortex surrenal dans la periode post-natale, chez de chien, *Compt. rend Soc. biol*, Paris, *145*.1060, 1951
18 Jailer, J W., *et al*. Pituitary-adrenal relationship in infants *J. Clin. Endocrinol & Metab*, *11*.186, 1951.
19 Venning, E H. Adrenal function in the newborn in pituitary-adrenal function A publication of the American Association for the Advancement of Science, Washington, D C, 1951, p. 149
20 Ingle, D J. Functional interrelationship of the anterior pituitary and adrenal cortex *Ann Int. Med*, *35* 652, 1951.
21. Ingle, D J. Effects of administering large amounts of cortin on adrenal cortices of normal and hypophysectomized rats *Am J. Physiol*, *124* 369, 1938.
22 Sydnor, K. L, Sayers, G, Brown, H, and Tyler, F. H Preliminary studies on blood ACTH in man. *J Clin. Endocrinol. & Metab*, *13* 891, 1953
23 Sydnor, K L, Kelley, V. C, Raile, R. B., Ely, R S, and Sayers, G *Blood adrenocorticotrophin in children with congenital adrenal* hyperplasia *Proc Soc Exper. Biol & Med*, *82* 695, 1953
24 Deane, H W. Physiological regulation of the zona glomerulosa of the rat's adrenal cortex, as revealed by cytochemical observations, in pituitary-adrenal function A publication of the American Association for the Advancement of Science, Washington, D C, 1950, p 31
25 Wilkins, L, Crigler, J F, Jr, Silverman, S H, Gardner, L I, and Migeon, C J. Further studies on the treatment of congenital adrenal hyperplasia with cortisone III The control of hypertension with cortisone, etc *J. Clin Endocrinol & Metab*, *12* 1015, 1952
26. Blackman, S S., Jr Concerning the function and origin of the reticular zone of the adrenal cortex *Bull Johns Hopkins Hosp*, *78* 180, 1946
27 *Forbes, A P, and Albright, F Comparison of 17-ketosteroid ex*cretion in Cushing's syndrome associated with adrenal tumor and with adrenal hyperplasia *J Clin Endocrinol*, *11* 926, 1951
28 Engel, F L The anterior pituitary and adrenal cortex *Ann Rev Physiol*, *15* 397, 1953
29 Ingle, D J Control of Regeneration of the Adrenal Cortex in the Rat, in Pituitary-Adrenal Function (A A A S, 1949) Baltimore, The Horn-Schafer Company, 1951, p 49
30 Renold, A E, Jenkins, D, Forsham, P H, and Thorn, G W The use of intravenous ACTH A study in quantitative adrenocortical stimulation *J Clin Endocrinol & Metab*, *12* 763, 1952

63 Kass, E. H, Ingbar, S. H, and Findland, M · Effects of adrenocorticotrophic hormone in pneumonia. Clinical, bacteriological, and serological studies. *Ann Int. Med*, *33* 1081, 1950

64 Mogabgab, W T, and Thomas, L · The effects of cortisone on experimental infection with Group A streptococci in rabbits *Proc Soc Clin Res*, 23.75, 1950

65. Antopol, W., Quittner, H, Gittler, R, Dordick, J, and Sophra, I.· The occurrence of spontaneous infections after the administration of cortisone and ACTH *Bull. New York Acad M*, 28 540, 1952.

66 Antopol, W., and Quittner, H · The changing pattern of infectious processes under the influence of cortisone. *J. Mount Sinai Hosp*, *19* 91, 1952

67. The influence of hormones on enzymes (Editorial) *Ann New York Acad Sci*, *54* Article 4, Dec. 1951.

68 Thorn, G. W, Forsham, P H, Prunty, F T G, and Hills, A G Test for adrenal cortical insufficiency response to pituitary adrenocorticotropic, *J.A M.A*, *137* 1005, 1948

69 Godlowski, Z. Z The fate of eosinophils in hormonally induced eosinopenia and its significance *J Endocrinol*, *8* 102, 1952

70 Padawer, J and Gordon, A S · A mechanism for the eosinopenia induced by cortisone and by epinephrine *Endocrinology*, *51* 52, 1952.

71. Ingle, D. J, Morley, E H, and Nezamis, J E The work performance of normal rats given continuous intravenous injections of cortisone and of corticotropin *Endocrinology*, 51 487, 1952

72. Cuthbertson, D P. Observations on the disturbance of metabolism produced by injury to the limbs *Quart J Med*, *1* 233, 1932

73 Heard, R D H, and Sobel, H A colorimetric method for the estimation of reducing steroids *J Biol Chem*, *165* 687, 1946

74 Robbie, W A, and Gibson, R B Rapid clinical determination of urinary 17-ketosteroids *J Clin Endocrinol*, 3 200, 1943

75 Bonsnes, R W, and Taussky, H H On colorimetric determination of creatinine by Jaffe reaction *J Biol Chem*, *158* 581, 1945

76 White, A, and Dougherty, T F Role of adrenal cortex and thyroid in mobilization of nitrogen from tissues in fasting *Endocrinology*, *41* 230, 1947

77 Blount, H C, Jr, and Hardy, J D Thyroid function and surgical trauma, as evaluated by iodine conversion ratio *Am J Med Sci*, 224 112, 1952

78 Goldenberg, Ira S, and Hayes, M A *Thyroid Adrenocortical Relationships During Surgical Convalescence* Fundamental Forum, 1953. Philadelphia, W B Saunders Company, in press

47 Davis, J O., and Howell, D. S : Comparative effect of ACTH, cortisone, and DCA on renal function, electrolyte excretion and water exchange in normal dogs *Endocrinology*, *52*.245, 1953
48 Levitt, M F., and Bader, M. E : Effect of cortisone and ACTH on fluid and electrolyte distribution in man *Am J. Med*, *11*.715, 1951.
49 Robinson, F. J, Kepler, E. J., and Power, M. H.: Two new procedures to assist in the recognition and exclusion of Addison's disease, a preliminary report. *Proc. Staff Meet, Mayo Clinic*, *16*.577, 1941
50 Sartorius, O W, Calhoon, D, and Pitts, R. F. Studies on the interrelationships of the adrenal cortex and renal ammonia excretion of the rat *Endocrinology*, *52* 256, 1953.
51 Roberts, K E, and Pitts, R F. The influence of cortisone on renal function and electrolyte excretion in the adrenalectomized dog *Endocrinology*, *50* 51, 1952
52 Cooke, R E, Segar, W. E, Cheek, D B, Coville, F E., and Darrow, D C The extrarenal correction of alkalosis associated with potassium deficiency *J Clin Invest*, *31* 798, 1952
53 Grad, B The influence of ACTH on the sodium and potassium concentration of human mixed saliva *J. Clin Endocrinol & Metab*, *12* 708, 1952
54 Johnson, H T, Conn, J W, Iob, V, and Coller, F A Postoperative salt retention and its relation to increased adrenocortical function *Ann Surg*, *132* 374, 1950
55 Hardy, J D The role of the adrenal cortex in the postoperative retention of salt and water Ann Surg, 132 189, 1950
56 Hardy, J D Relationships between fever and sweating, *Federation Proc*, *11* 64, 1952
57 Hardy, J D, and Ravdin, I S Some physiologic aspects of surgical trauma *Ann Surg*, *136* 345, 1952
58. Streeten, D H P, and Ward-McQuaid, J H Relation of electrolyte changes and adrenocortical activity to paralytic ileus *Brit M J*, 2 587, 1952
59 Robson, H N, and Duthie, J J R Capillary resistance and adrenocortical activity *Brit M J*, 2 971, 1950
60 Kramar, J, and Simay-Kramar, M, The effect of adrenalectomy, surgical trauma, and ether anesthesia upon the capillary resistance of the albino rat *Endocrinology*, *52* 453, 1953
61 Hoagland, H Pituitary-adrenocortical function in patients with severe personality disorders, in pituitary-adrenal function A publication of the American Association for the Advancement of Science, 1951, p 202
62 Cook, C, and Smith, C Sepsis and cortisone *Nature*, *170* 980 1952

93 Perry, W. F, and Gemmell, J P. The effect of surgical operations on the excretion of iodine, corticosteroids, and uric acid *Canad. J. Research*, 27.320, 1949

94 Schoen, I, Strauss, L, and Bay, M. W · An evaluation of the eosinophil count in patients undergoing major surgery *Surg, Gynec. & Obst*, *96* 403, 1953

95. Krupp, M. A, Engleman, E P, Welsh, J. E, and Wrenn, H T Measurement of the excretion of cortisone and compound F, using the Porter-Silber method. *J Clin Endocrinol & Metab*, *12* 1163, 1952

96 Hardy, J. D, Cole, F. H, Gragg, W H, Jr, and Wilson, F C, Jr. Metabolic reaction to staged operations in man *Am J. Physiol*, *171* 3, 1952 (abstract).

97 Hardy, J D, and Cole, F. H The metabolic reaction to staged operations in man. Fundamental Forum, 1953. Philadelphia, W B Saunders Company, p 536

98 Evans, E I, and Butterfield, W J H. The stress response in the severely burned *Ann Surg*, *134* 588, 1951

99 Wight, A, Raker, J W, Merrington, W R, and Cope, O The ebb and flow of the eosinophils in the burned patient and their use in the clinical management *Ann Surg*, *137* 175, 1953

100 Heller, A L, and Shipley, R A Endocrine studies in aging *J Clin Endocrinol & Metab*, *11* 945, 1951

101 Meyer, R J · Relative insensitivity of the hypothalamic-pituitary-adrenal system to activation by epinephrine *J Clin Endocrinol & Metab*, *13* 123, 1953

102 Wilkins, L, Lewis, R A, Klein, R, and Rosemberg, E The suppression of androgen secretion by cortisone in a case of congenital adrenal hyperplasia *Bull Johns Hopkins Hosp*, *86* 249, 1950

103 Hardy, J D, Alley, F H, Jones, R S, and Bowerman, E P Surgical management of adrenocortical tumors *Am Surgeon*, *19* 833, 1953

104 Hardy, J D Urinary steroids in adrenocortical tumor *Ann Surg*, *138* 765, 1953

105. Christian, J J The relation of adrenal weight to body weight in mammals *Science*, *117* 78, 1953

106 Talbot, N B Physiology of adrenal cortex *Pediatrics*, *3* 519, 1949

107. Cushing, Harvey The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism) *Bull Johns Hopkins Hosp*, *50* 137, 1932

108 Dohan, F C, Rose, E, Eiman, J W, Richardson, E M, and Zintel, H Increased urinary estrogen excretion associated with adrenal tumors Report of 4 cases *J Clin Endocrinol & Metab*, *13* 415, 1953

79 Hardy, J. D, Richardson, E. M., and Dohan, F. C.: The urinary excretion of corticoids and 17-ketosteroids following major operations Correlation with other aspects of metabolism. *Surg, Gynec & Obst*, *96* 1, 1953.

80. Moore, F. D, and Ball, M. R: *The Metabolic Response to Surgery.* Springfield, Thomas, 1952.

81 Stevenson, J. A. F, Schenker, V, and Browne, J. S L The 17-ketosteroid excretion in damage and convalescence. *Endocrinology*, *35* 216, 1944.

82 Venning, E. H, Hoffman, M. M, and Browne, J. S L · The extraction of cortin-like substances from human postoperative urine *Endocrinology*, *35* 49, 1944

83. Venning, E H, and Browne, J. S L: Urinary excretion of adrenal cortical steroids. *Ann. N Y. Acad Sc*, *50* 627, 1949

84 Mason, A L, and Engstrom, W. W.: The 17-ketosteroids their origin, determination, and significance. *Physiol. Rev*, *30* 321, 1950.

85 Nelson, D H, Samuels, L. T, Willardson, D G, and Tyler, F H: The levels of 17-hydrocorticosteroids in peripheral blood of human subjects *J Clin Endocrinol & Metab*, *11* 1021, 1951

86 Nelson, D H, and Samuels, L T. A method for the determination of 17-hydroxycorticosteroids in blood 17-hydroxycorticosterone in the peripheral circulation *J Clin Endrocrinol & Metab*, *12* 519, 1952.

87 Danford, P A, and Danford, H G: The effect of water and potassium chloride ingestion on the level of urinary 17-ketosteroids in the rabbit *Endocrinology*, *47* 139, 1950

88 Nathanson, I T, Engel, L L, and Kelley, R. M The effect of androgens on the urinary excretion of ketosteroids, nonketonic alcohols, and estrogens *J Clin Endocrinol & Metab*, *12* 1172, 1952

89. Mason, H L Determination of 17-ketosteroids *J Clin Endocrinol & Metab*, *13* 1009, 1953

90. Bacchus, H, and Heiffer, M H Urinary corticosteroids and 17-ketosteroids in adrenalectomized female rats treated with cortisone and ascorbic acid *Am J Physiol*, *173* 33, 1953

91. Shadaksharappa, K, Calloway, N O, Kyle, R H, and Keeton, R W Excretion of steroidal substances by the adrenal cortex in various diseases *J Clin Endocrinol*, *11* 1383, 1951

92 Kenigsberg, S, and McGavack, T H The excretion of 17-ketosteroids II Values in several endocrine disturbances *J Clin Endocrinol. & Metab*, *12* 1551, 1952

124. Venning, E. H, and Browne, J. S. L.. Effect of testosterone on the excretion of glycogenic corticoids. *J. Clin Endocrinol*, *7* 729, 1947.

125 Williams, R H. Hyperadrenocorticism *Am J Med*, *10* 612, 1951

126. Teabeaut, R, Engel, F. L., and Taylor, H M. Hypokalemic alkalosis in Cushing's syndrome. Observations on the effects of potassium chloride and testosterone (Abstract) *J Clin Endocrinol*, *9* 663, 1949.

127. Willson, D. M, Power, M. H, and Kepler, E. J. Alkalosis and low plasma potassium in a case of Cushing's syndrome *J Clin Investigation*, *19* 701, 1940

128. McQuarrie, I, Johnson, R. M, and Ziegler, M R Plasma electrolyte disturbance in a patient with hypercorticoadrenal syndrome contrasted with that found in Addison's disease *Endocrinology*, *21*.762, 1937.

129 Priestley, J. T., Sprague, R G, Walters, W, and Salassa, R M Subtotal adrenalectomy for Cushing's syndrome, a preliminary report of 29 cases *Ann Surg*, *134* 464, 1951

130 Walters, W. Subtotal adrenalectomy for Cushing's syndrome *Arch Surg*, *66* 244, 1953

131 Kupperman, H S, Bernstein, A, Forbes, A, Cope, O, and Albright, F. Remission in Cushing's syndrome after bilateral hemiadrenalectomy. *J Clin Endrocrinol. & Metab*, *13* 154, 1953

132 Rose, E K, Enterline, H T, Rhoads, J E, and Rose, E Adrenal cortical hyperfunction in childhood, report of a case with adrenocortical hyperplasia and testicular adrenal rests *Pediatrics*, *9* 475, 1952

133. Gordan, G. S, and Hinman, F, Jr Mortality in surgically treated adrenocortical tumors II Review of cases reported for the 20-year period 1930-1949, inclusive *Postgrad Med*, *11* 325, 1952

134. Wilkins, L, Gardner, L I, Crigler, J F, Jr, Silverman, S H., and Migeon, C J Further studies on the treatment of congenital adrenal hyperplasia with cortisone I Comparison of oral and intramuscular administration of cortisone, with a note on the suppressive action of compounds F and B on the adrenal *J Clin Endocrinol & Metab*, *12* 257, 1952

135 Wilkins, L, Crigler, J F, Jr, Silverman, S H, Gardner, L I, and Migeon, C. J Further studies on the treatment of congenital adrenal hyperplasia with cortisone II The effects of cortisone on sexual and somatic development, with an hypothesis concerning the mechanism of feminization *J Clin Endocrinol & Metab*, *12* 277, 1952

109 Wilkins, L · Hyperadrenocorticism. *Pediatrics,* 3 533, 1949
110. Wilkins, L · The diagnosis of sexual abnormalities. *J. Clin Endocrinol. & Metab*, 13.369, 1953.
111 Simpson, S L. Pituitary-adrenal hyperfunction. *Proc. Roy Soc Med*, 46 39, 1953.
112 Forbes, A, and Albright, F A comparison of the 17-ketosteroid excretion in Cushing's syndrome associated with adrenal tumor and with adrenal hyperplasia. *J. Clin Endocrinol & Metab*, 11 928, 1951
113 Jailer, J W, Louchart, J, and Cahill, G F: Adrenal virilism I Diagnostic considerations and treatment. *J. A M A*, 150 575, 1952.
114 Gardner, L I, and Migeon, C J. Le diagnostic des tumeurs virilisantes du cortex surrenalien. effet de la cortisone sur les steroides urinaires et utilisation d'une methode colorimetrique pour le dosage de la dehydroisoandrosterone. *Helvet Paediat acta*, 6 465, 1951.
115 Venning, E H, Pattee, C J, McCall, F., and Browne, J S L Effect of cortisone on the excretion of 17-ketosteroids in adrenal tumor *J Clin Endocrinol & Metab*, 12 1409, 1952
116 Gardner, L I, and Migeon, C J. Urinary dehydroisoandrosterone in hyperadrenocorticism influence of cortisone, hydrocortisone, and ACTH *J Clin Endocrinol & Metab*, 12 1117, 1952
117 Jailer, J W, Louchart, J, Gold, J J, and Knowlton, A I The effect of cortisone on the urinary excretion of 17-ketosteroids in patients with Cushing's syndrome *J. Clin Investigation*, 32 449, 1953
118 Effect of cortisone on excretion of 17-ketosteroids in adrenal virilism and simple hirsutism (Editorial) *Lancet, 1* 1287, 1952
119 Bastenie, P A, Franckson, J R M, Verbiest, M, Kovacs, L, and Flamand, C Cortisone treatment in adrenogenital syndrome *Lancet, 1* 915, 1953
120. Jailer, J W A fluorometric method for the clinical determination of estrone and estradiol J Clin Endocrinol, 8 564, 1948
121 Landau, R L, Clark, D E, and Stimmel, B Gynecomastia and retarded sexual development resulting from a long-standing estrogen-secreting tumor (Abst) *J Clin Endocrinol & Metab*, 12 915, 1952
122 Venning, E H., and Browne, J S L Excretion of glycogenic corticoids and of 17-ketosteroids in various endocrine and other disorders J Clin Endocrinol, 7 79, 1947
123 Bartter, F. C, Forbes, A P, Jefferies, W M, Carroll, E L, and Albright, F The mechanism of action of testosterone in the therapy of Cushing's syndrome (Abstract) *J Clin Endocrinol*, 9 663, 1949.

152. Thorn, G W., Goetz, F. C, Streeten, D H P, Dingman, J F, and Arons, W L. Use of intravenous ACTH test in clinical practice *J Clin. Endocrinol. & Metab*, *13* 604, 1953
153 Thorn, C. W Measurement of adrenal cortical function (Editorial) *J. Clin Endocrinol. & Metab*, *13* 614, 1953.
154. Butterly, J M, Fishman, L, Seckler, J, and Steinberg, H. Addison's disease secondary to metastatic carcinoma of the adrenal glands · *Ann Int Med*, 37.930, 1952
155 Newman, L. R · Waterhouse-Friderichsen syndrome Report of cure effected with cortisone *J A M A*, *146* 1229, 1951
156 Nelson, J, and Goldstein, N Nature of Waterhouse-Friderichsen syndrome *J.A M.A*, *146*.1193, 1951.
157 Hume, D M, and Moore, F D The use of ACTH, cortisone, and adrenal cortical extracts in surgical patients Second Clinical ACTH Conference, Edited by John R. Mote, Blakiston, 1951, p 289
158. Cole, W. H, Grove, W J, and Montgomery, M M Use of ACTH and cortisone in surgery *Ann Surg*, *137* 718, 1953
159 Koppel, D M Treatment of exfoliative dermatitis with cortisone *U. S Armed Forces M J*, *4* 607, 1953
160. Thedos, P A Bronchography in iodine sensitivity *J A M A*, *148* 1419, 1952
161. Scheinberg, S R, and Saltzstein, H C Effect of cortisone and corticotrophin (ACTH) on intra-abdominal adhesions *Arch Surg*, *63* 413, 1951
162. Scheinberg, S R, Saltzstein, H C, and Johnson, A S. The prevention of adhesions in the chest and pericardium by cortisone Surgical Forum, Am Coll Surgeons Philadelphia, W B Saunders Company, 1951, p 531
163 Odell, R T, Key, J A, and Taylor, L W The prevention of peritoneal adhesions and the granulomata by cortisone, a preliminary report Surg Forum, Am Coll Surgeons Philadelphia, W B Saunders Company, 1951, p 524
164 Hufay, C A, Meckesser, E C, and Holden, W D The effect of cortisone on the prevention of peritoneal adhesions *Surg*, *Gynec & Obst*, *96* 65, 1953
165 Hart, F D, Wraith, D G, and Mansell, E J B Agranulocytosis successfully treated with ACTH *Brit M J*, *1* 1273, 1952
166 Agranulocytosis (Editorial) *Brit M J*, *1* 553, 1953
167 Meyers, M C, Miller, S, and Bethell, F H Administration of ACTH in hypersplenic syndrome *J Lab & Clin Med*, *36* 965, 1950.

136. Gastineau, C F., Logan, B. G, Albert, A., and Mason, H L: Use of cortisone for congenital adrenal hyperplasia in the male Report of a case. *J. Clin Endocrinol. & Metab*, *13*.724, 1953
137. Kelly, V. C, Ely, R. S, and Raile, R. B: Metabolic studies in patients with congenital adrenal hyperplasia Effects of cortisone therapy *J Clin Endocrinol & Metab.*, *12*.1140, 1952.
138. Hubble, D · Treatment of the adrenogenital syndrome with cortisone *Lancet*, *2* 464, 1952.
139. Zuelzer, W W, and Blum, A. Adrenocortical insufficiency in infants with the adrenogenital syndrome *J. Pediat*, *35* 344, 1949
140 Butler, A M., Ross, R A, and Talbot, N B.. Probable adrenal insufficiency in an infant *J Pediat*, *15* 831, 1939.
141 Doxiadis, S A Adrenogenital syndrome with insufficiency of the electrolyte-regulating function of the adrenal cortex. *Proc. R Soc Med*, *45* 587, 1952
142 White, F P, and Sutton, L E Adrenogenital syndrone with associated episodes of hypoglycemia *J Clin Endocrinol & Metab*, *11* 1395, 1951
143 Wilkins, L, Fleischmann, W, and Howard, J E Macrogenitosomia precox associated with hyperplasia of the androgenic tissue of the adrenal and death from corticoadrenal insufficiency, a case report *Endocrinology*, *26* 385, 1940
144 Wilkins, L A feminizing adrenal tumor causing gynecomastia in a boy of five years contrasted with a virilizing tumor in a five year-old girl *J Clin Endocrinol*, *8* 11, 1948
145 Baxter, H, Schiller, C, Whiteside, J H, and Randall, R E Use of ACTH and cortisone in surgery *Am J Surg*, *83* 374, 1952
146 Kinsell, L W The clinical application of pituitary adrenocorticotropic and adrenal steroid hormones *Ann Int Med*, *35* 615, 1951
147 Holley, H L, and Riser, W H, Jr The indications and contraindications for cortisone and adrenocorticotropic hormone therapy *Am Practitioner*, *3* 368, 1952
148 Boland E D Clinical use of cortisone, hydrocortisone and corticotropin *J A M A*, *150* 1281, 1952
149 Pincus, G E F The dose response in man to oral and injected lipo-adrenal cortical extract *J Clin Endocrinol & Metab*, *12* 642, 1952
150 Cochrane, G C, John, J P, Foreman, N and Kinsell, L W Evaluation of adrenal steroids administered by different routes *J Clin Endocrinol & Metab*, *13* 993, 1953
151 DeMowbray, R R, and Bishop, P M F ACTH in diagnosis of adrenal insufficiency (Thorn test) *Brit M J*, *1* 17, 1953

152 Thorn, G W, Goetz, F. C, Streeten, D H. P, Dingman, J. F, and Arons, W. L: Use of intravenous ACTH test in clinical practice *J. Clin Endocrinol & Metab*, *13* 604, 1953

153 Thorn, G. W.· Measurement of adrenal cortical function (Editorial) *J Clin Endocrinol & Metab*, *13* 614, 1953.

154 Butterly, J. M, Fishman, L, Seckler, J, and Steinberg, H Addison's disease secondary to metastatic carcinoma of the adrenal glands *Ann. Int. Med.*, 37.930, 1952.

155 Newman, L R Waterhouse-Friderichsen syndrome· Report of cure effected with cortisone *J.A M A*, *146* 1229, 1951.

156. Nelson, J, and Goldstein, N · Nature of Waterhouse-Friderichsen syndrome. *J A M A*, *146* 1193, 1951.

157. Hume, D M, and Moore, F. D. The use of ACTH, cortisone, and adrenal cortical extracts in surgical patients Second Clinical ACTH Conference, Edited by John R. Mote, Blakiston, 1951, p 289.

158. Cole, W. H, Grove, W. J, and Montgomery, M M Use of ACTH and cortisone in surgery *Ann Surg*, *137* 718, 1953

159 Koppel, D. M Treatment of exfoliative dermatitis with cortisone *U. S. Armed Forces M. J*, *4* 607, 1953

160 Thedos, P. A. Bronchography in iodine sensitivity *J A M A*, *148* 1419, 1952.

161 Schemberg, S. R, and Saltzstein, H. C Effect of cortisone and corticotrophin (ACTH) on intra-abdominal adhesions *Arch Surg*, 63.413, 1951

162 Schemberg, S R, Saltzstein, H C, and Johnson, A S The prevention of adhesions in the chest and pericardium by cortisone Surgical Forum, Am Coll Surgeons. Philadelphia, W B Saunders Company, 1951, p 531

163 Odell, R T, Key, J A, and Taylor, L. W The prevention of peritoneal adhesions and the granulomata by cortisone, a preliminary report Surg Forum, Am Coll Surgeons Philadelphia, W B Saunders Company, 1951, p 524.

164 Hufay, C A, Meekesser, E C, and Holden, W D The effect of cortisone on the prevention of peritoneal adhesions *Surg, Gynec & Obst*, *96* 65, 1953

165 Hart, F. D., Wraith, D G, and Mansell, E J B Agranulocytosis successfully treated with ACTH *Brit M J*, *1* 1273, 1952

166. Agranulocytosis. (Editorial) *Brit M J*, *1* 553, 1953

167. Meyers, M C, Miller, S, and Bethell, F H Administration of ACTH in hypersplenic syndrome *J Lab & Clin Med*, *36* 965, 1950.

168 Kiernan, P C, and Hunter, O. B, Jr.: The use of ACTH in hypersplenism. Surg. Forum, Am. Coll. Surgeons. Philadelphia, W. B. Saunders Company, 1951, p. 83.
169 Faloon, W W., Greene, R W., and Lozner, E. L: The hemostatic defect in thrombocytopenia as studied by the use of ACTH and cortisone. *Am J Med*, *13*:12, 1952.
170 Evans, R. S., and Liu, C K.: Effect of corticotrophin on chronic, severe primary thrombocytopenic purpura. *Arch. Int Med*, *88* 503, 1951
171 Jacobson, B. M, and Sohier, W D: The effects of ACTH and of cortisone on the platelets in idiopathic thrombopenic purpura *New England J. Med*, *246*:247, 1952
172 Meyers, M C, Miller, S, Linman, J W., and Bethell, F H. The use of ACTH and cortisone in idiopathic thrombocytopenic purpura and idiopathic acquired hemolytic anemia *Ann Int Med*, *37* 352, 1952
173 Dameshek, W, Rosenthal, M C, and Schwartz, L I The treatment of acquired hemolytic anemia with adrenocorticotrophic hormone (ACTH) *New England J. Med*, *244* 117, 1951
174 Crary, H I, and Beck, I A · Idiopathic acquired hemolytic anemia treated with ACTH and cortisone *Ann Int Med*, *36* 1106, 1952
175 Aitchison, J D Hemolytic anemia treated by ACTH, cortisone, and splenectomy *Brit M J*, *1* 78, 1953
176 Sacks, M S, Workman, J B, and Jahn, E F Diagnosis and treatment of acquired hemolytic anemia *J A M A*, *150* 1556, 1952
177 Welch, C S, and Dameshek, W "Emergency" splenectomy? (Editorial) *Surg, Gynec & Obst*, *95* 521, 1952
178 Raker, J W, Wight, A, Michel, A J D, and Cope, O A clinical and experimental evaluation of the influence of ACTH on the need for fluid therapy of the burned patient *Ann Surg*, *134* 614, 1951
179 Hollander, J L, Brown, E M, Jr, Jessar, R A, and Brown, C Y Hydrocortisone and cortisone injected into arthritic joints *J A MA*, *147* 1629, 1951
180 Ebert, R H, and Barclay, W R Changes in connective tissue reaction induced by cortisone *Ann Int Med*, *37* 506, 1952
181 Orbach, E J Bursitis and myofascitis, treatment by local injections of cortisone a preliminary report *J Internat Coll Surgeons*, *17* 19, 1952
182 Steinberg, C L, and Roodenburg, A I Corticotropin (ACTH) in the treatment of acute subacromial bursitis *J A M A*, *149* 1458, 1952
183 Orbach, E J Treatment of bursitis by local injection of hydrocortisone acetate *J Internat Coll Surgeons*, *18* 159, 1952

184. Quigley, T. P., and Renold, A E.: Acute calcific tendinitis and frozen shoulder, their treatment with ACTH *New England J Med*, *246* 1012, 1952.

185. Stein, I, Stein, R. O, and Beller, M L. ACTH in postmanipulative phase of frozen shoulder *Am J Surg*, *85* 215, 1953.

186. Kierland, R. R., and Hines, E. A, Jr: Cortisone and corticotrophin (ACTH) in treatment of scleroderma. *Arch. Dermat. & Syph*, *64* 549, 1951.

187. Ritchey, S J The use of cortisone in Dupuytren's contracture. *U S. Armed Forces J M*, 3.811, 1952.

188 Briggs, J N., and Illingworth, R. S Calcinosis universalis treated with adrenocorticotrophic hormone and cortisone *Lancet*, *2* 600, 1952.

189 Daw, W J., and Funke, A H. Osteitis pubis treated with cortisone *J. Urol*, *69* 686, 1953

190 Davis, T. A., and Zeller, M.: Multiple peptic ulcers with massive hemorrhage during oral cortisone therapy, report of a case. *J A M A.*, *150* 31, 1952

191 Habif, D. V, Hare, C C, and Glaser, G H Perforated duodenal ulcer associated with pituitary adrenocorticotropic hormone (ACTH) therapy *J.A M.A*, *144* 996, 1950

192 Davenport, H W, and Chavre, V J The lack of effect of the adrenal hormone upon gastric acid secretion *Endocrinology*, *47* 193, 1950.

193. Gray, S J, Benson, J A, Jr, and Reifenstein, R W, Chronic stress and peptic ulcer I. Effect of corticotropin (ACTH) and cortisone on gastric secretion *J.A M A*, *147* 1529, 1951

194 Higgins, G A, and Rider, R D Bleeding gastric ulcer requiring partial gastrectomy in a patient receiving cortisone *Am Surgeon*, *19* 275, 1953

195 Kirsner, J. B, Klotz, A P, and Palmer, W L Unfavorable course of gastric ulcer during administration of ACTH and cortisone *Gastroenterology*, *20* 27, 1952

196. Kirsner, J B, and Palmer, W L Effect of corticotropin (ACTH) in chronic ulcerative colitis, observations in forty patients *J.A M.A*, *147* 541, 1951

197. Larkin, M A, and Flannery, M G Surgical experience with corticotropin in ulcerative colitis *Arch Surg*, *66* 386, 1953

198 Gray, S. J, Reifenstein, R W, and Benson, J A, Jr ACTH therapy in ulcerative colitis and regional enteritis *New England J. Med*, *245* 481, 1951

199. Gray, S J, Reifenstein, R. W., Young, J C. G, and Benson, J. A, Jr.: The use of ACTH in the treatment of ulcerative colitis and regional enteritis Second Clinical ACTH Conference, Edited by John R Mote Philadelphia, Blakiston, 1951, p 473.

200. Brown, G. M, and McAuley, J S.: Cortisone therapy in ulcerative colitis. *J A M A*, *150* 1587, 1952.

201. Halsted, J A. The effects of ACTH and cortisone in diseases of the digestive system. Med Clin North America, p 1069, July, 1952

202 Tulin, M, Kern, F, Jr, and Almy, T P: Perforation of bowel during treatment of ulcerative colitis, report of three cases *J A M A*, *150*.559, 1952.

203 Sauer, W G, Grown, P W, and Dearing, W. H.. Experiences with the use of corticotropin in regional enteritis *Gastroenterology*, 22 550, 1952

204 Webster, J J: Adrenal cortex in liver disease *Ann Int. Med*, 33 854, 1950

205. Ripkin, H, *et al* Use of corticotropin and cortisone in acute homologous serum hepatitis *Arch Int Med*, *89* 32, 1952

206 ACTH and cortisone in infective hepatitis (Editorial) *Brit M J*, *1* 860, 1952

207 Stephenson, H E, Jr, Pfeffer, R. B, and Saypol, G M Acute hemorrhagic pancreatitis, report of a case with cortisone treatment *Arch Surg*, *65* 307, 1952

208 Ellison, E H, Martin, B C, Williams, R D, Clatworthy, H W, Hamwr, G, and Zollinger, R M The effect of ACTH and cortisone on the survival of homologous skin grafts *Ann Surg*, *134* 495, 1951

209 Weisman, P A, Quinby, W C, Jr, Wight, A, and Cannon, B The adrenal cortical hormones and homografting, exploration of a concept. *Ann Surg*, *134* 506, 1951

210 Weisman, P A, Wight, A, Quinby, W C, Jr, and Cannon, B The failure of adrenal cortical hormones to prolong the survival of homologous skin grafts *Plastic & Reconstruct Surg*, *8* 417, 1951

211 Conway, H, Stark, R B, Joslin, D, and Docktor, J P The development of circulation in autogenous and homologous grafts of skin and observations upon the effects of ACTH and anticoagulants Surg Forum, Am Coll Surgeons Philadelphia W B Saunders Company, 1951, p 468

212 Randall, P, Brown, J B, and McDowell, F The effects of ACTH and cortisone on experimental skin grafts Surg Forum, Am Coll Surgeons Philadelphia, W B Saunders Company, 1951, p 475

213 Bishop, R. C, Beal, J. M., and Longmire, W P., Jr The use of ACTH and cortisone in homografting, effect of preoperative administration of ACTH to donor and recipient on the survival of skin homografts in humans *West J Surg*, *60* 193, 1952
214 Martin, B C, Morgan, T W., and Lovingood, C G The effect of ACTH on autogenous and homologous skin grafts in rabbits *Surgery, 31* 258, 1952
215 Kay, J H. The influence of cortisone and ACTH on the survival of adrenal homotransplants in the dog *Surgery, 32* 686, 1952.
216 Szilagyi, D E, Margulis, R R, and Jay, G. D Observations on effects of corticotropin (ACTH) and cortisone in management of some postoperative surgical problems *Arch Surg*, *65* 217, 1952
217. Larson, D L, and Tomlinson, L G Quantitative antibody studies in man. I. The effect of adrenal insufficiency and of cortisone on the level of circulating antibodies *J Clin Investigation, 30* 1451, 1951
218. Boling, L, Newkirk, J, Baxter, P, Partridge, J, Margen, S, and Kinsell, L. W.: *The use of ACTH in the management of generalized peritonitis J Clin Endocrinol & Metab*, *12* 184, 1952
219. Garrison, S C Encephalomyelitis complicating antirabies vaccination treated with cortisone *Am J Med*, *12* 135, 1952
220 Martin, S P, Schwartz, T B, and Engel, F. L The effect of adrenal hormone therapy on the course of infectious diseases *North Carolina M J*, *13* 605, 1952
221 Lee, R E, and Pfeiffer, C C Effects of cortisone and 11-desoxycortisone on pain thresholds in man *Proc. Soc Exper Biol & Med*, *77* 752, 1951
222 Fromer, J L, and Smith, A I The use of ACTH in ten patients with severe anogenital pruritis *Lahey Clin Bull*, *7* 232, 1952
223 Turrell, R. Corticotropin and cortisone in intractable anogenital pruritis *J A M A*, *152* 806, 1953
224 Russek, H I, Russek, A S, Doerner, A A, and Zohman, B L: Cortisone in treatment of shoulder-hand syndrome following acute myocardial infarction *Arch Int Med*, *91* 487, 1953
225 Scheinberg, L C Tetanus treated with cortisone *U S Armed Forces M J*, *3* 1377, 1952
226 Spector, S and Mercer, R D The effect of pituitary adrenocorticotrophic hormone on experimental tetanus in mice *J Infect Dis*, *89* 224, 1951
227 Christensen, N A, Keith, H M, Smith, L A, Hanson, N O, and Ralston, D E Cortisone in the treatment of tetanus, report of a case *Proc Staff Meet*, *Mayo Clin*, *27* 28, 1952
228 Maretic, Z Arachnidism treated with cortisone *J A M A*, *152* 609, 1953.

229. Feldman, D J, and Zucker, H. D.: Present-day management of alcoholism *J.A.M.A*, *153*,895, 1953
230 Fischback, K, Simmonds, E. M, and Pollard, H E.: *Delirium tremens treated with intravenously administered corticotropin (ACTH) J A M A*, *149* 927, 1952.
231. Lecoq, R. Action comparee des effects de l'hormone adrenocorticotrope (ACTH) et de la cortisone avec quelques facteurs enzymatiques sur l'intoxication alcoholique experimentale, *Compt rend Soc biol*, *145* 1600, 1951.
232 Rose, E, and Boles, R S, Jr. Hypercalcemia in thyrotoxicosis. *Med. Clin North America, 37* 1715, 1953
233 Kinsell, L W, Partridge, J W., and Foreman, N · The use of ACTH and cortisone in the treatment and in the differential diagnosis of malignant exophthalmus. *Ann Int Med*, *38*,913, 1953
234 Tate, W. M, and Wheeler, J A. Temporal arteritis report of a case with ACTH therapy *J Kansas M Soc*, *52* 374, 1951
235 Schulman, S, and Bergenstal, D Treatment of temporal arteritis with cortisone a case report *Ann Int Med*, *37* 1088, 1952
236 Aveling, J V, and Stevenson, F H Temporal arteritis treated with ACTH *Lancet*, *2* 610, 1952
237 Whitfield, A G W, Cooke, W. D., Jameson-Evans, P, and Rudd, C · Temporal arteritis and its treatment with cortisone and ACTH *Lancet*, *1* 408, 1953
238 Shick, R M, Baggenstoss, A M, Fuller, B F, and Polley, H F. Effects of cortisone and ACTH on periarteritis nodosa and cranial arteritis. *Proc. Staff Meet*, *Mayo Clin*, *25* 492, 1950.
239 Jacques, R H Thrombo-angiitis obliterans treated with cortisone, report of a case *Ohio M J*, *48* 620, 1952.
240 Howard, J M, and DeBakey, M E The treatment of hemorrhagic shock with cortisone and vitamin B_{12} *Surgery*, *30* 161, 1951
241 Halpern, B N, Benacerraf, B, and Briot, M Effect protecteur de la cortisone dans le choc hemorrhagique, traumatique et toxique chez l'animal surrenalectomise, synergie potentialisatrice avec l'adrenaline *Compt rend Soc biol*, *145* 1770, 1951
242 Moore, H, and O'Donovan, D K Anuria treated by cortisone *Brit M J*, *1* 183, 1953
243 Soffer, L F, Gabrilove, J L, and Wolf, B S Effect of ACTH on thymic masses *J Clin Endocrinol & Metab*, *12* 690, 1952
244 Clarkson, P, Cortisone as an adjunct to surgery in the treatment of keloids *Lancet*, *1* 923, 1953
245 LeMaistre, C, and Tompsett, R The evaluation of tuberculous lesions in the guinea pig during administration of adrenocorticotropic hormone (ACTH) and cortisone *Am Rev Tuberc*, *64* 295, 1951

246. Kleinschmidt, R F, and Johnston, J. M.. Miliary tuberculosis in a cortisone treated patient. case report with autopsy. *Ann Int Med*, *35* 694, 1951.

247. Deleterious effect of ACTH and cortisone on tuberculosis (Editorial) *New England J. Med*, *245* 662, 1951.

248. Traut, E F., and Ellman, J.· Exacerbation of tuberculosis during treatment with cortisone *J.A M.A*, *149*.1214, 1952

249 Hulbert, N. G. Miliary tuberculosis in a case of acute disseminated lupus erythematosus treated with ACTH. *Proc. Roy Soc Med*, *45* 167, 1952.

250 Effect of cortisone and/or corticotropin on tuberculous infection in animals, a statement prepared by the committee on therapy *Am Rev Tuberc*, *66* 257, 1952.

251. Bunim, J J., Kaltman, A. J, and McEwen, C. Diabetogenic effect of cortisone and ACTH in a non-diabetic patient with rheumatoid arthritis. *Am. J Med*, *12*·125, 1952

252. DeCosta, E. J, and Abelman, M. A Cortisone and pregnancy, an experimental and clinical study of the effects of cortisone on gestation. *Am. J. Obst. & Gynec*, *64* 746, 1952

253 Gulbeau, J A, Jr. Effects of cortisone on the fetus *Am J Obst & Gynec*, *65* 227, 1953

254 Fraser, F. C, and Fainstat, T D Production of congenital defects in the offspring of pregnant mice treated with cortisone, progress report *Pediatrics, 8 527, 1951*

255 Sprague, R. C, Power, M H, Mason, H L, Albert, A, Mathieson, D R, Hench, P. S, Kendall, E C, Slocumb, C H, and Polley, H. F.· Observations on the physiologic effects of cortisone and ACTH in man *Arch Int Med*, *85* 199, 1950

256 Iatrogenic adrenal insufficiency (Editorial) *J A M A., 150* 1222, 1952.

257 Engleman, E P, Krupp, M A, Johnson, H P, Jr, Welsh, J E, Wrenn, H T., and King, W R - Adrenocortical function during continuous long-term therapy with cortisone. *Arch Int Med*, *91*·1, 1953

258 Fraser, C G, Preuss, F S, and Bigford, W D Adrenal atrophy and irreversible shock associated with cortisone therapy *J A M A*, *149* 1542, 1952.

259. McIntosh, H. W, and Holmes, C B Some evidence suggesting the suppression of adrenocortical function with cortisone *Lancet*, 2 1061, 1951

260 Wilson, L A Protein shock from intravenous ACTH *Lancet*, 2 478, 1951

261. Mogabgab, W J, and Thomas, L The effects of cortisone on bacterial infection *J Lab and Clin Med*, 39 271, 1952

262 Steinberg, H, Webb, W M, and Rafsky, H. A · Hepatomegaly with fatty infiltration secondary to cortisone therapy· case report. *Gastroenterology, 21* 304, 1952.

263 Homes, E L, *et al* · Retardation of wound healing by cortisone *Surgery, 28* 177, 1950.

264 Taylor, F. W, Dittmer, T L, and Porter, D. O Wound healing and the steroids. *Surgery, 31* 683, 1952.

265 Haley, R, and Laws, J F The effect of cortisone on wound healing, blood regeneration, and growth Surg. Forum, Am Coll. Surgeons, Philadelphia, W B. Saunders Company, 1951, p. 488

266 Sissons, H A, and Hadfield, G. J The effect of cortisone on the regeneration of skeletal muscle after injury. *J Bone Surg*, Brit, *35-B*· 1, 125

267 Muller, W H, Jr, Spencer, F. C, and Lewis, A E. The effect of cortisone on the healing of wounds of the cardiovascular system *Surgery*, 33 399, 1953

268 Shepanek, L A The effect of endocrine substances (ACTH and growth hormone) on experimental fractures. *Surg*, *Gynec. & Obst*, *96* 200, 1953

269 Sissons, H A, and Hadfield, G J The influence of cortisone on the repair of experimental fractures in the rabbit. *Brit. J Surg*, 39 172, 1951.

270 Teicher, R, and Nelson, C. T Osteoporosis and pathological fractures following treatment with ACTH and cortisone *J Invest Dermat*, *19* 205, 1952

271 Cosgriff, S W Thromboembolic complications associated with ACTH and cortisone therapy. *J A M A., 147* 924, 1951

272 Greeman, L, Weigand, F A, and Danowski, T S Cation exchange resin therapy in patients receiving cortisone or ACTH *Am J Med Sc*, 225 1, 1953

273. Kinsell, L W, Partridge, J W, Boling, L, and Margen, S. Dietary modification of the metabolic and clinical effects of ACTH and cortisone *Ann. Int Med*, *37* 921, 1952

274 Kinsell, L W, *et al* Modification of the clinical and metabolic effects of ACTH by dietary means. *J Clin Endocrinol & Metab*, *11*.1031, 1951

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